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SPECIAL MEDICAL SERVICE IN THE DEFENSE PROGRAM *

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THE effects of war or preparation for defense have always posed special service problems for medical men, for wherever the armies of the many warring Nations have fought there also the soldier-surgeon-physician, men of genius like Ambrose Paré, Dominique Larry, Sir John Pringle, Sir Ronald Ross, Major Walter Reed, and countless others, have carried their skills to the battlefields in an effort to prevent illness and to mitigate the suffering of the wounded.

The whole map of this World War is being so speedily reshaped by the ebb and flow of British naval might and German military power that it is of the utmost importance that at least a few of the special service problems confronting the military surgeon be catalogued and brought to the attention of the leaders in the civil medical profession; for without your coöperation, the Army and Navy medical officers will be handicapped.

The Franco-Prussian War of 1870 provides the first record of a war in which more men were lost from military action than from disease. A similar record was established in the Russo-Japanese War of 1904. Despite the epidemic of influenza in 1918, the World War I was the first war in which the forces of the United States had fewer deaths from disease than from battle casualties, although for the entire Army at home and overseas, the deaths from disease were preëminent.[1]

In order to emphasize the importance of communicable diseases, it is well to review briefly some of the experiences of the 1914–1918 World War and to indicate what may be expected in event unfortunate contingencies force upon this Nation the mobilization of large numbers of men.

* Read at the Boston meeting of the American College of Physicians, April 24, 1941.

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In the United States Army * for the period 1914–1918, the largest number of primary admissions for the communicable diseases was recorded for influenza, venereal diseases, mumps and measles. Influenza, tuberculosis, measles, and cerebrospinal meningitis were the leading causes of death.

Table 1 shows the number of primary admissions, the rates per 1,000, and days lost from duty for the U. S. Army from April 1, 1917, through December 31, 1919, in all areas of the United States, Alaska, and Europe, exclusive of Russia. The total mean annual strength of the U. S. Army was 4,128,479, with 2,235,389 in the United States and 1,665,796 in Europe.

Table 2 contains the same information for the U. S. Navy for the calendar years 1917, 1918, and 1919.

Infections of the respiratory tract were among the leading causes of sickness and death in both the Army and the Navy during this period.

TABLE I

Admissions and Days Lost from Duty for Certain Infectious Diseases, U. S. Army,[1] Apr. 1, 1917–Dec. 31, 1919

	Primary Admissions		Days Lost from Duty	
	Number	Annual Rate per 1,000	Number Sick Days	Noneffective Ratio per 1,000 [2]
Respiratory diseases [3]	1,125,401	272.6	17,042,838	11.3
United States	749,004	335.1	9,368,434	11.5
Europe	335,484	201.4	7,306,906	12.0
Influenza	791,907	191.8	10,676,172	7.1
United States	533,649	238.7	6,146,574	7.5
Europe	228,461	137.2	4,296,815	7.1
Bronchitis	255,148	61.8	3,287,643	2.2
United States	169,426	75.8	1,543,152	1.9
Europe	76,975	46.2	1,669,261	2.8
Pneumonia (all)	78,346	19.0	3,079,023	2.0
United States	45,929	20.5	1,678,708	2.1
Europe	30,048	18.0	1,340,830	2.2
Venereal diseases (all)	357,969	86.7	6,804,818	4.5
United States	284,742	127.4	4,745,450	5.8
Europe	57,195	34.3	1,748,067	2.9
Gonococcus infection	251,899	61.0	3,903,303	2.6
United States	211,638	94.7	2,867,491	3.5
Europe	31,199	18.7	891.492	1.5
Syphilis (all)	67,026	16.2	1,927,901	1.3
United States	51,528	23.0	1,345,961	1.6
Europe	12,680	7.6	511,657	.8
Chancroidal infection	39,044	9.5	973,614	.6
United States	21,576	9.6	531,998	.6
Europe	13,316	8.0	344,918	.6
Mumps	230,356	55.8	3,884,147	2.6
United States	141,628	63.4	2,276,544	2.8
Europe	81,853	49.1	1,501,222	2.5
Measles	98,225	23.8	1,877,944	1.2
United States	85,398	38.2	1,600,798	2.0
Europe	9,168	5.5	229,745	.4

* All Army figures, unless otherwise specified, are from the Medical Department of the U. S. Army in the World War Medical and Casualty Statistics, 1925, Government Printing Office.

TABLE I (*Continued*)

	Primary Admissions		Days Lost from Duty	
	Number	Annual Rate per 1,000	Number Sick Days	Noneffective Ratio per 1,000 [2]
Dysentery (all), diarrhea, enteritis, and colitis	92,512	22.4	1,060,229	.7
United States	39,854	17.8	232,241	.3
Europe	48,202	28.9	793,972	1.3
Tuberculosis of lungs	33,249	8.0	3,385,053	2.2
United States	27,274	12.2	2,636,722	3.2
Europe	4,877	2.9	677,169	1.1
German measles	17,378	4.2	211,645	.1
United States	16,167	7.2	197,330	.2
Europe	579	.4	8,505	[4]
Malarial fevers (all)	15,555	3.8	194,529	.1
United States	10,510	4.7	130,673	.2
Europe	950	.6	20,477	[4]
Scarlet fever	11,675	2.8	498,190	.3
United States	9,038	4.0	382,628	.5
Europe	2,370	1.4	106,877	.2
Diphtheria	10,909	2.6	317,050	.2
United States	5,884	2.6	144,452	.2
Europe	4,860	2.9	168,100	.3
Meningitis, cerebrospinal (epidemic)	4,831	1.2	268,164	.2
United States	2,878	1.3	150,386	.2
Europe	1,848	1.1	114,110	.2
Chickenpox	1,757	.4	31,534	[4]
United States	1,208	.5	21,443	[4]
Europe	388	.2	7,582	[4]
Typhoid fever	1,529	.4	109,374	.1
United States	546	.2	28,587	[4]
Europe	885	.5	76,649	.1
Smallpox	853	.2	24,275	[4]
United States	780	.4	21,890	[4]
Europe	24	[4]	1,110	[4]
Trench fever	798	.2	34,098	[4]
United States	11	[4]	674	[4]
Europe	786	.5	33,402	[4]

[1] Total mean annual strength = 4,128,479; United States (including Alaska) = 2,235,389; Europe (excluding Russia) = 1,665,796; other (Philippine Islands, Panama, etc.) = 227,294.

[2] $\text{Noneffective rate} = \dfrac{\text{total days lost} \times 1{,}000}{\text{total mean annual strength}} \div 365$

[3] Respiratory diseases include influenza, bronchitis, lobar and broncho-pneumonia and pneumonia, unclassified.

[4] Rate per 1,000 less than 0.1.

Influenza, bronchitis, and pneumonia combined were responsible for 1,326,306 admissions, giving a rate of 256.21 per 1,000. There were 50,042 deaths, or a death rate of 9.67 per 1,000, and a case fatality rate of 3.8 per cent. These diseases accounted for 19,293,711 sick days during this period, or a noneffective ratio of 10.03 per 1,000.* The 10 diseases responsible for the greatest number of sick days in the Army and Navy are listed in table 3. A total of 39,082,365 sick days was recorded for these diseases.

* Reports of Surgeon General, U. S. Navy, for 1918, 1919, and 1920.

TABLE II

Admissions and Days Lost from Duty for Certain Infectious Diseases, U. S. Navy, Calendar Years 1917, 1918, and 1919

Disease	Primary Admissions		Days Lost from Duty	
	Number	Annual Rate per 1,000	Number Sick Days	Noneffective Ratio per 1,000
Respiratory diseases	200,959	191.73	2,250,873	5.87
Influenza	151,916	144.94	1,366,625	3.57
Bronchitis	32,525	31.03	374,989	0.98
Pneumonia (all)	16,518	15.76	509,259	1.33
Venereal diseases (all)	90,790	86.53	1,248,488	3.26
Gonococcus infection	56,155	53.58	647,326	1.69
Syphilis	13,350	12.74	398,858	1.04
Chancroidal infections	20,995	20.03	202,304	0.53
Mumps	33,485	31.95	630,126	1.64
Measles	15,687	14.97	224,909	0.59
Dysentery (all), diarrhea, enteritis and colitis	6,399	6.11	67,916	0.18
Tuberculosis	4,180	3.99	569,683	1.49
German measles	6,389	6.10	84,998	0.22
Malarial fevers (all)	7,327	6.99	103,257	0.27
Scarlet fever	2,594	2.47	102,847	0.27
Diphtheria	2,858	2.73	75,522	0.20
Meningitis, cerebrospinal (epidemic)	408	.39	17,118	0.04
Cerebrospinal fever	1,065	1.02	69,563	0.18
Chickenpox	618	.59	12,434	0.03
Typhoid fever	167	.16	10,001	0.03
Smallpox	91	.09	2,786	0.007
Trench fever	3	.003	42	0.0001

The 10 leading causes of death for the U. S. Army for the years 1917, 1918, and 1919 are of interest to the student of this problem.†

The health of the Navy has long been of interest to the civilian practitioner who seldom appreciates the complexity of the peculiar circumstances of Naval service. The wartime increase in the Navy between 1917 and 1919 was accompanied by the widespread occurrence of measles, mumps, and influenza. Influenza alone was responsible for more deaths than all other communicable diseases combined. The explosive epidemic of cerebrospinal fever which occurred at the Naval Training Station, Great Lakes, Illinois, in 1918 was accompanied with a high fatality rate. Of the communicable diseases, influenza, pneumonia (all forms), cerebrospinal fever, and tuberculosis led the group as causes of death.

The Navy's influenza epidemic of 1918 afloat began in the Atlantic Fleet and reached its peak in about ten days. It is now believed that many of the deaths charged to pneumonia during this epidemic should properly have been charged to influenza. A study of the influenza epidemic in the ships of the Navy shows that with few exceptions the personnel afloat suffered much less than personnel ashore, in spite of the fact that almost all the ships of the Navy were overcrowded and that the crews of transports were exposed

† Reports of Surgeon General, U. S. Army, for 1918, 1919, and 1920.

TABLE III

Ten Leading Causes of Disability as Expressed by Numbers of Sick Days

Army	Sick Days [1]	Navy	Sick Days [2]
Influenza	10,676,172	Influenza	1,366,625
Gonorrhea	3,903,303	Gonorrhea	647,326
Mumps	3,884,147	Mumps	630,126
Tuberculosis (lungs)	3,385,053	Tuberculosis	569,683
Bronchitis	3,287,643	Pneumonia (all)	509,259
Pneumonia (all)	3,079,023	Syphilis	398,858
Syphilis	1,927,901	Bronchitis	374,989
Measles	1,877,944	Measles	224,909
Dysentery (all)	1,060,229	Chancroid	202,304
Chancroid	973,614	Malaria (all)	103,257
Total	34,055,029	Total	5,027,336

[1] April 1, 1914 to December 31, 1918.
[2] Calendar years 1917, 1918 and 1919.

to epidemic conditions incident to outbreaks of a highly virulent form of influenza among troops in transit. As a rule, the epidemic attack rate on board ship was comparatively low, 16.3 per cent for battleships, 26.2 per cent for submarines and destroyers, and 8.8 per cent for transports. The epidemic death rate on battleships was 7.3 per 1,000; on submarines and destroyers 7.9 per 1,000; and on transports 2.2 per 1,000.

There were, however, notable exceptions such as the U. S. S. *Pittsburgh*, which encountered the disease in Rio de Janeiro and had approximately 80 per cent of its personnel affected. The U. S. S. *Yacona* furnished another exception with approximately 80 per cent of its personnel attacked. The origin of the epidemic of influenza on board the U. S. S. *Yacona* was New London, Connecticut.

A partial explanation of the variation in the rates for influenza afloat and ashore is that the Fleet is largely protected by a quarantine of recruits for about eight weeks at a Naval Training Station before the men are transferred to sea. The Naval Training Stations are also more exposed to infection from contact with civilians, which invites epidemic invasion.

TABLE IV

Ten Leading Causes of Death, United States Army. Death Rates per 1,000

1917		1918		1919	
Measles	1.44	Influenza (all)	9.14	Influenza (all)	1.76
Lobar pneumonia	1.20	Lobar pneumonia	3.34	Tuberculosis (all forms)	1.50
Meningitis (epidemic)	.50	Bronchopneumonia	2.71	Bronchopneumonia	1.37
Bronchopneumonia	.36	Measles	.59	Lobar pneumonia	1.02
Crushing	.22	Meningitis (epidemic)	.47	Meningitis (epidemic)	.34
Suicide	.21	Tuberculosis (all forms)	.38	Fracture, compound	.21
Tuberculosis (all forms)	.20	Pneumonia, unclassified	.18	Fracture, simple	.18
Drowning	.15	Crushing	.18	Crushing	.16
Appendicitis	.12	Bronchitis	.17	Suicide	.15
Fracture, simple	.09	Fracture, compound	.17	Appendicitis	.12

For the Navy as a whole, there were 102,847 sick days from scarlet fever and 75,522 sick days from diphtheria for the years 1917, 1918, and 1919. Navy ships may visit ports where health authorities have neglected widespread immunization and should serious overcrowding again become necessary, there is every reason to expect that this experience will be repeated.

Following a recent epidemic of diphtheria in Halifax an extensive survey revealed the fact that only one person in five was immune to the disease. Immunity was no higher in the military and naval forces in and about the city. Inquiry reveals that there is a general belief among health officials that most adults are immune. The incidence rate for diphtheria has been low in both Canada and the United States for several years, and the health authorities have not been much concerned over possible epidemics from this disease. It is reasonable to believe, however, that large numbers of men of military age in the United States are non-immunes. Fortunately, this disease can be quickly controlled by widespread immunization with diphtheria toxoid. This method of control will greatly reduce the carrier problem which prevailed in 1918.

The ten leading causes of morbidity and mortality for the U. S. Navy for the years 1917, 1918, and 1919 appear in tables 5 and 6.

TABLE V

Ten Leading Causes of Morbidity, U. S. Navy. Admission Rates per 1,000

1917		1918		1919	
Gonococcus infection.	58.38	Influenza	240.62	Tonsillitis, acute	69.98
Tonsillitis, acute	50.54	Tonsillitis, acute	47.29	Gonococcus infection.	68.32
Influenza	42.04	Gonococcus infection.	42.49	Influenza	68.17
Mumps	39.82	Mumps	35.40	Bronchitis	40.66
Measles	31.33	Bronchitis	30.17	Chancroid	26.84
Bronchitis	21.09	Pneumonia (all)	24.99	Mumps	19.66
Chancroid	20.28	Wounds, gunshot	17.05	Syphilis	16.47
German measles	16.56	Chancroid	15.87	Abscess, unclassified.	10.98
Abscess, unclassified.	10.64	Measles	13.73	Contusions	10.00
Syphilis	10.05	Syphilis	11.83	Cellulitis	8.80

TABLE VI

Ten Leading Causes of Death, U. S. Navy. Death Rates per 1,000

1917		1918		1919	
Pneumonia (all)	0.81	Influenza	8.25	Influenza	1.87
Drowning	.79	Wound, gunshot	3.64	Drowning	0.71
Cerebrospinal fever	.46	Drowning	1.89	Tuberculosis (all)	.60
Tuberculosis (all)	.25	Pneumonia (all)	1.50	Pneumonia (all)	.32
Pleurisy	.23	Cerebrospinal fever	0.41	Wounds, punctured	.22
Meningitis	.21	Tuberculosis (all)	.26	Fracture, skull	.18
Wounds, gunshot	.19	Injuries, multiple, extreme	.24	Injuries, multiple, extreme	.15
Fracture, skull	.15	Measles	.22	Cerebrospinal fever	.10
Exhaustion	.13	Fracture, skull	.20	Burns	.09
Injuries, multiple, extreme	.12	Burns	.18	Nephritis	.09

It should be remembered that the preparation for defense or the waging of war has always been attended by an increase in the prevalence and often a shocking increase in the virulence of disease. This is brought about by the rapid spread of infection incident to conditions of mobilization and transport of combat troops from widely separated parts of the world. In the civil population of Europe, now subjected to all the hazards of war, fatigue, famine, lack of sanitation, and inadequate medical care are the detonators for explosive epidemics. Just when the epidemic explosion may be expected is a matter of grave concern to epidemiologists.

The late Hans Zinsser,[2] basing his reasoning on experiences in the mobilization camps in 1917, pointed out that outbreaks of epidemics are almost inevitable when large numbers of men from all over the country are brought together in camps under circumstances which call for arduous physical and disciplinary training. Much control over the epidemic intestinal diseases such as typhoid and dysentery can be exerted by suitable preventive measures, but the situation with regard to respiratory diseases is more difficult. In such conditions as measles and mumps neither prevention nor treatment can be much better controlled than formerly.

Zinsser was convinced that the unimpeded flare-up of infectious diseases among young military units is stimulated by two factors: the too rapid bringing together of large numbers of susceptible young men with large numbers of carriers of the various respiratory organisms and the quite natural but too energetic efforts to force military training and the physical hardening process at a pace too strenuous for the relatively soft recruit.

Military mobilization presents a challenge and an opportunity. Available epidemiologic information must be utilized in planning each step of the assembly and care of the new recruits. The behavior of epidemic disease under the different circumstances which develop must be carefully recorded and analyzed. Only by immediate concentration on these two objectives will it be possible to profit fully from the unique epidemiologic opportunity furnished by mobilization.[3]

Since the war of 1914–1918, there has been a general strengthening of many public health measures, such as child health, tuberculosis, and the control of communicable disease including venereal disease control programs. The major success of these efforts is based on reporting, yet the reporting of disease is so unsatisfactory in the civil communities that Dr. Gallup [4] has seen fit to take a nation-wide poll on the extent of last winter's epidemic of colds and "flu" and concludes as follows: "The probable dimensions of the last winter's flu epidemic are indicated for the first time in a survey by the American Institute of Public Opinion. Questions put to a cross-section of several thousand men and women in all parts of the country—the results of which will be of particular interest to the medical profession—point to the following conclusions:

" 1. That fully a fourth of the adult population suffered from flu or grippe during the last winter. When this figure is applied to the total adult population of more than 80 millions, the Institute survey indicates that at least 20 million adult Americans were affected between October and March.

" 2. This survey did not include persons under 21 years of age which would mean an additional 12 or 13 million cases, assuming the same rate of incidence as among the older people.

" 3. Inadequacy of the normal health records on the subject is indicated by the fact that only one person in three who reported having had the flu said he had called a physician. The remainder said they had doctored themselves—either because ' it wasn't serious enough to call a doctor ' or ' because we couldn't afford one.' "

This poll further reports: " For the first time in United States history it has been possible to chart the extent of America's No. 1 health problem—colds and flu.

" More than 50,000,000 adults suffered from colds. More than 20,000,000 were affected by flu. The reason, of course, is that most cases of flu —and the overwhelming majority of colds—are simply never reported to doctors and health authorities.

" Here are findings from the Institute Survey which will give medical and health authorities some of the first evidence ever obtained on the incidence and cost of the two ailments throughout the 48 States. This means that more than 50,000,000 adults suffered loss of vitality, efficiency or working time because of colds in the last six months. . . . Assuming the same rate of incidence among those under 21, the results point to a total of about 84,000,000 who were affected. The combined replies indicated a total loss of approximately 59,000,000 working days for employers and employees, laborers and white-collar workers."

It would be of tremendous advantage to disease control programs if the profession would inaugurate a campaign to require adequate reporting of communicable diseases. This campaign might well be organized by a concerted effort on the part of the press, radio, medical societies and health organizations to encourage the population of our large cities to report such conditions as colds, grippe, etc., to their Health Departments. The information would be of great value in the much needed epidemiological study of influenza.

Malaria

It is of interest to note that there were 15,555 admissions for malaria in the U. S. Army during the period April 1, 1917, to December 31, 1919, and of this number 10,510 occurred among troops in the United States. There were 7,327 cases of malaria in the U. S. Navy for the calendar years 1917, 1918, and 1919, the majority of which were contracted in Haiti and

Santo Domingo. Due to the acquisition of the new Bases, there is excellent reason to predict an increase in the number of cases of malaria among the military forces. The reason for this apprehension is that malaria is endemic in some of the areas where the Bases are to be located and the native populations will be difficult to control.

Should this prediction fail, it will be due entirely to the fact that the Army and Navy medical forces and the health agencies have been able to accomplish a huge task of malaria control.

The importation of large numbers of troops and civilian workmen to these Bases presents a real problem now because malaria carriers may start an epidemic and thus delay the construction of the Bases and the training of the troops. Of civilian concern is the return of these troops and laborers to their home communities. There is the ever-present prospect that some of them may become carriers and serve as a focus of an epidemic of malaria in areas where malaria has not existed for many years. There is a real shortage of competent medical and engineering personnel to handle malaria control problems for the armed forces and an equally important shortage of experienced medical personnel to cope with a malaria epidemic in an area previously free from this disease. For several years malariologists have noted the occurrence of malaria in areas in the United States free of the disease and many have speculated on the possibility of a return of malaria to these areas.

It is advisable to redirect the teaching of malariology in the medical schools and to encourage the strengthening of the malaria control units in key localities to prevent unnecessary deaths from malaria. There is need for intensive research on a more simple but reliable method of diagnosis, such as a precipitin test or skin reaction. The armed forces need a vaccine against malaria or a reliable drug for prophylaxis. Little progress has been made in the chemotherapy of malaria since the introduction of atabrin.

Yellow Fever

Since one insect-borne disease has been mentioned it is advisable to invite attention to the fact that yellow fever cannot be dismissed from the problems which must be met. It is now known that the "jungle type" of yellow fever is endemic in certain tropical areas and that at least one important outbreak of the disease has occurred in the Anglo-Egyptian Sudan. Little official information is available on this epidemic.

Yellow fever has for several years been a matter of concern to the National and some State health organizations because of the increase in airplane travel and the possibility that either infected travellers or infected mosquitoes introduced into the United States might result in a very dangerous situation.

It is reassuring to know that a vaccine is now available which produces lasting immunity, that it is available in considerable quantities, and that facilities for its manufacture can be speedily expanded.

The Army and Navy are vaccinating both the military and civilian populations ordered to areas where yellow fever may be endemic.

Venereal Diseases

Colonel Harrison's "Venereal disease nausea" aptly summarizes the attitude in the higher reaches and the cloistered sectors of far too much of the world's medical profession to a group of communicable diseases which have been prime wasters of military man power for centuries. This unfortunate attitude is apt to increase and will further delay the control of syphilis and gonorrhea. No group of people thinking of emergency service can overlook this vexatious question.

From whatever viewpoint considered, the venereal diseases present the largest problem in preventive medicine confronting the military surgeon. They surpass in magnitude and administrative significance all other communicable diseases and, to make a bad matter worse, the research funds devoted to the study of these diseases are pitifully small.

The U. S. armed forces in World War I lost 7,492,510 sick days, or the equivalent of nearly 20,600 men for a whole year. Expressed in terms of ship complement, there were enough days lost to man five aircraft carriers and nine World War destroyers.

It should be remembered that the Army and Navy reject for enlistment—and for Navy industrial employment—men suffering from venereal diseases. The subsequent damage comes from the civil populations and this and other official medical bodies can and should do much to reduce venereal disease incidence in the civilian population. Just one measure—law enforcement—would go far to reduce military damage from venereal diseases.

Surgeon General Parran has performed a magnificent public service—even though he has annoyed many complacent medical men—by focusing attention on the gravity of syphilis as a health problem and breaking down the prudish taboos preventing free and open discussion of this problem.

Infectious Diseases in the Present World War

Epidemiologists both in the United States and abroad are handicapped because of the lack of current information on the world picture of communicable diseases during the present World War, and it is expected that these data will decrease rather than increase due to political and military mandates. Since this condition exists, it seems fitting to review briefly what is known.

Up to the present, mild influenza and cerebrospinal meningitis have been the most notable infections occurring in the warring nations. A general decline in incidence of cerebrospinal meningitis has been noted throughout Europe since World War I, although there have been cyclical increases on an 8 to 12 year cycle. There was a general rise in this disease in the United States, reaching its peak in 1936. In 1939 and 1940 the occurrence of cerebrospinal meningitis was extremely widespread in Europe and Great Britain. The number of cases reported seems to have been without precedent in recent years.

Typhus is showing increased activity in eastern Europe,[1] Spain,[5] and China.[6] An increase of typhus was noted in 1939 and 1940 in parts of Turkey, Bulgaria, and Yugoslavia,[5] and more recent unofficial information indicates that there is a sharp rise in Poland and parts of Russia. The disease has appeared in parts of Germany, where it has not been endemic, notably in East Prussia and Polish Silesia. There was a small epidemic in Mecklenburg in March 1940.

An outbreak of dysentery comparable with that of World War I was reported in the German Army during the Polish Campaign of 1939 [1] and in the French prison camps in 1940.[5]

In 1939, out of a total of 15 countries in the War Zone, 7 showed some increase in typhoid fever, as did Australia, Japan, and the United States.[1] It is expected that typhoid fever will remain a relatively minor problem in the armed forces of the United States at home, but increasing vigilance is necessary in the newly acquired Bases and in military and industrial concentrations.

The movement of population which occurred in England when the War began in 1939 was the greatest since the time of the Great Plague of 1665, when London was emptied of about 2/3 of its population. The total evacuation is reported to be in excess of 1,270,000, including children, expectant mothers, and the blind and crippled.[5] This changed environment was expected to result in an increased prevalence of the communicable diseases. Inadequate sanitation, heating, and ventilation, and overcrowding of the bomb shelters and temporary quarters complicated the health problem and were thought to invite the spread of certain diseases. Increased foci for tuberculosis resulted from the limitation in hospitalization of the tuberculous. An unusually severe winter, shortage of fuel, and the black-out conditions encouraged the spread of respiratory infections. These factors augmented the health hazards of war resulting from mobilization, air raids, changes in work hours and dietary habits, lack of sleep, nervous strain, and increased fatigue especially noted among the industrial workers.

Fortunately, there has not been the general increase in infectious diseases that was predicted at the beginning of the battle of Britain. The incidence of respiratory infections was somewhat higher than usual, but there was a significant reduction in the number of reported pneumonia deaths. This has been attributed to the use of sulfanilamide and related compounds.[7]

Both influenza and cerebrospinal meningitis have been widespread. Influenza is not a notifiable disease in England, hence the incidence record of this disease is in the same class as the American experience. The number of reported deaths from influenza up to March 1940 was higher than the expectancy for the season. Influenzal pneumonia is being reported.

Previous reporting of cerebrospinal fever in England and Wales has never approached the 1939–40 figures.[1] The unofficial reports for the first six weeks of 1941 indicate about the same degree of prevalence. Case fatal-

ity varies greatly in different parts of the country, but on the whole is much less than in 1914–18 when the fatality among civilians was about 60 per cent and in some localities as high as 80 per cent. Case fatality for the 1939–40 [1]–41 [7] period is from 10 to 12 per cent. However, private reports indicate a mortality of 30 per cent from children groups in certain communities.

An Associated Press despatch dated January 7, 1941,[8] quoted Sir William Jamison, Chief Medical Officer of the Health Ministry, as reporting increases of cerebrospinal meningitis, pneumonia, typhoid fever, and dysentery for England and Wales for the year 1940.

Conflicting opinions are encountered on the incidence of neuropsychiatric disorders and this uncertainty will probably remain until the official figures are released.

The latest published information from Great Britain (1940)[1] indicates that the health of the Army is good except for epidemics of German measles, influenza, and cerebrospinal fever. The occurrence of cerebrospinal fever was sporadic and showed a fatality rate markedly lower than for the War of 1914–18. Certain treatment centers are reporting an increase in venereal disease, but the prevalence in the defense forces is not considered comparable with the early stages of World War I.

What Should Be Done

Due to the geographic location of the United States and the present focus of war, none of the organizations of the warring nations is quite applicable to the American form of government or to the mental attitude of our people. Large areas of this country obviously need no protection, either because they contain no vital industrial facilities or they are so sparsely populated that no foreign power would waste aircraft and other costly weapons upon them. However, almost every large community has vital activities, such as industrial establishments, transportation centers, and administrative offices, and they would be considered worth the attention of the parachutist, alien saboteur, or a few bombs. In each of these localities effective organization of both protective and medical facilities is necessary, not only to save life but for the effect on national morale.

The fullest possible use should be made of existing local, state and national official organizations, such as the Red Cross, Boy Scouts, American Legion, etc. The police and fire departments should be the nucleus of the local civilian organization.

Suggested Organization for the City or Local Government:

(1) The evacuation.
(2) Transportation, ambulances, private cars, boats, drivers.
(3) Public utilities. Security, maintenance, and repair of power system. Water and sewage systems, gas and telephone systems.
(4) Regional food depots.

(5) Bomb-proof shelters.
(6) Casualty services:
  (*a*) First-aid posts.
  (*b*) Hospitals. The expansion of existing hospitals. The construction of new facilities.
  (*c*) Shock and hemorrhage service. Plasma production.
(7) Special services:
  (*a*) Communications.
  (*b*) Reporting. Liaison.
(8) Fire:
  (*a*) From incendiary bombs.
  (*b*) Ordinary fire protection.
(9) Police:
  (*a*) Ordinary law enforcement.
  (*b*) Specially trained persons for the detection of saboteurs.
(10) Sanitation:
  (*a*) Usual supervision.
  (*b*) Decontamination of gassed areas.
(11) Disaster relief:
  (*a*) Emergency care of wounded.
  (*b*) Care of the dead.
  (*c*) Rescue.
  (*d*) Demolition of unsafe structures.
  (*e*) Road clearance and maintenance.
(12) Personnel:
  (*a*) Physicians, nurses, dentists, stretcher bearers, laboratory and other technicians, orderlies, and clerks.
(13) Equipment and supplies.

The details of the local functions are obvious and need no further elaboration, but organization should be such as to meet the anticipated needs of the local situation.

Suggested Organization for the State Government:

(1) The transportation and care of the chronically ill, hospital populations, and all evacuées.
(2) A greatly augmented statistical service for the handling of morbidity and mortality statistics (these data should be current and receive wide administrative distribution.)

(3) The rapid evacuation of civilians whose occupations are not essential to the efficient operation of the country should an air attack warning be received is one of the obvious services to be rendered in order that the maximum use might be made of hospitals and medical services for possible wounded. This would include the children, the old, the infirm, and expectant mothers.

What Has Been Done

Almost a year ago, April 26, 1940, the Surgeons General of the Army and Navy invited the Division of Medical Sciences of the National Research Council to "stand by" to assist the Armed Services in preparing for the emergency.[9] About the middle of May, 1940 the Surgeons General of the Army and Navy requested Dr. Lewis H. Weed, Chairman of the Division of Medical Sciences, National Research Council to establish special committees to act in an advisory capacity to the two Armed Services. At the early meetings of these committees, many problems relating to other branches of medicine and pertinent to military affairs were presented and it was quickly realized that it would be necessary to appoint committees to explore the whole field of medicine. In all, seven main committees have been appointed, under which 34 sub-committees are operating.

The meetings of these committees are attended by liaison officers from the several military and civil agencies requiring their services. These committees have accomplished a splendid service, including the preparation of many Manuals and recommendations, and the service will be expanded with the acquisition of additional funds.

The American Medical Association has undertaken the huge task of determining the number of physicians available for service, the codification and classification of their special training, and other pertinent data.

The Health and Medical Committee was established by Order of the Council of National Defense dated September 19, 1940. The Order reads: "It will be the responsibility of the Committee to advise the Council of National Defense regarding the health and medical aspects of National Defense and to coördinate health and medical activities affecting National Defense." This Committee was transferred to the Federal Security Agency on November 28, 1940. The order of transfer stated, ". . . such committee shall hereafter exercise its duties and functions under the direction and supervision of the Federal Security Administration. . . ." This Committee has appointed six sub-committees, one of the most important of which is the Subcommittee on Industrial Health and Medicine. The deliberations of this Subcommittee have produced recommendations which will result in the improvement of industrial health practices and reduce illness from manufacturing processes.

The Navy is engaged in an intensive program of training medical officers in industrial hygiene and industrial medicine. When their training is com-

plete it is planned to set up an Industrial Hygiene and Industrial Medicine unit in each Naval District, to investigate industrial health conditions; submit recommendations; and, when approved, supervise the installation of improvements to reduce the health and accident hazards in Naval industrial establishments.

The Army has established a Board for the investigation of influenza and other epidemic diseases. This Board is composed of Drs. Blake, Pepper, Warren, Doshez, Avery, Maxcy, and Goodpasture. Its function is to plan and recommend policy for the investigation of epidemic diseases. Under the Board there are Commissions on the following diseases:

(1) Epidemiological Survey, Chairman, Dr. Stanhope Bayne-Jones, Yale University.
(2) Measles, Chairman, Dr. Joseph Stokes, University of Pennsylvania.
(3) Meningitis, Chairman, Dr. Perrin H. Long, Johns Hopkins University.
(4) Pneumonia, Chairman (has not been appointed).
(5) Neurotrophic virus disease, Chairman, Dr. John Paul, Yale University.
(6) Hemolytic streptococcus infections, Chairman, Dr. Martin H. Dawson, Columbia University.
(7) Influenza, Chairman, Dr. Thomas Francis, Jr., New York University.

These Commissions are organized for active field duty in case of need.

The Navy is organizing epidemiological teams to work with the Division of Preventive Medicine, Bureau of Medicine and Surgery, and their function will be similar to that described for the Army.

The American Red Cross is coöperating with the Subcommittee on Blood Substitutes, of the National Research Council, to procure blood donors and to arrange for the manufacture of a supply of dried and liquid plasma for the Armed Services.

The Rockefeller Foundation has manufactured and has in store a supply of yellow fever vaccine for the use of the Army and Navy. In addition, the International Health Division of the Rockefeller Foundation, under the able leadership of Dr. W. A. Sawyer, has agreed to coöperate with the Army and Navy in sanitating the extra-cantonment areas of the newly acquired Bases and in such other advisory service as may be necessary and required.

Physicians for Britain

Great Britain's appeal for physicians through its National Red Cross has received the official approval of both the President and The Secretary of War in the following press releases, April 21, 1941:

"The British Red Cross has appealed through the American Red Cross for at least 1,000 young American doctors to help it meet an acute shortage of doctors in

British military and civilian hospitals. As President of the American Red Cross I heartily approve this request.

"When the British appeal came to my attention, I asked the opinions of the Surgeons General of the Army, Navy and Public Health Service. They join me in believing we should encourage eligible American doctors to volunteer for this humanitarian service with our British friends. I also am informed that the Division of Medical Sciences of the National Research Council, the American Medical Association, the American College of Surgeons and the American College of Physicians have offered their assistance to the American Red Cross in meeting this emergency.

"The young doctors whom Great Britain so desperately needs can do much to heal the wounds inflicted alike upon civilians and military in this cruel war. Those who volunteer will be enrolled by the British Red Cross and will work under the protection of the Red Cross Treaty of Geneva, a covenant which has been respected by belligerents since 1864.

"To any American doctor, who is eligible and able to go, service in this cause presents a splendid opportunity."

/s/ FRANKLIN D. ROOSEVELT

"In connection with the appeal of the British Red Cross to the American Red Cross for the assistance of at least 1,000 American Doctors, the question arises: Can we spare the men?

"Naturally we must look to our own interests in the light of the emergency which faces the world today. We shall need several thousand more doctors in our own Army. However, I feel that we should do all in our power to aid in obtaining these physicians, consistent with the needs of our own medical defense. I can see no objections, therefore, to the fulfillment of this request through the machinery of the American Red Cross.

"Doctors who volunteer would serve under the terms of the Red Cross Treaty of Geneva, a convention 77 years old and guaranteeing immunity of medical workers on the field of battle. Both Allied and Axis forces are signatory to this treaty. To my knowledge, the principles of this agreement never have been violated.

"I am in personal sympathy with the proposal that we provide Britain with doctors. If the British need doctors—and we know that they do—I believe we can and should provide them with some of ours."

/s/ HENRY L. STIMSON

The urgent appeal for at least 1,000 physicians to augment the British Medical Services is a need of prime importance. Due to the exigencies of the service it is desired that these men be under 40 years of age, unmarried, and eligible for entry into the armed services of the United States. They will not be expected to swear allegiance to Great Britain, but will serve the military services and civilian population both in England and the Empire. Their compensation will be comparable with that of a First Lieutenant in the U. S. Army. They will be licensed to practice in the Empire during their service and will be eligible for promotion, gratuities, and pensions.

Their physical, professional, and moral qualifications will be carefully judged by the Medical Sciences Division of the National Research Council, assisted by representatives of the American Medical Association, American College of Surgeons, American College of Physicians, and the American Red Cross. They will be certified for passport visa and their travel expense paid by Great Britain.

The question naturally arises " How many physicians of the age group and qualifications are available? " It has been estimated that there are fewer than 10,000 such men in the medical profession of the United States.

This appeal for medical assistance places squarely before this and other medical organizations a task that may require a revision of the medical, hospital, and teaching organizations of the whole country.

The writer desires to express his gratitude to Mrs. Laura T. Anderson, Senior Clerk, Bureau of Medicine and Surgery, Navy Department, for her editorial assistance in the preparation of this paper, and to Lieutenant (jg) George W. Mast (MC), U. S. Navy, and G. B. Peterson, Pharmacist's Mate, lcl, U. S. Navy, for their assistance in searching official records.

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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THE RECRUIT'S FIRST YEAR*

By P. S. Madigan, F.A.C.P., *Medical Corps, U. S. Army, Washington, D. C.*

Since the birth of our nation and the formation of a defensive army to protect our shores, it has forever been foremost in the minds of our military leaders to stress the point that the art of soldiering should be a vocation of life. Every vocation of necessity has its prerequisites, and the art of soldiering differs in no way from this general principle. Numerous writers throughout the history of our country have dilated upon this aspect in their description of military life.

During the present emergency it is incumbent upon the Army to train a million and a half soldiers. We must give these young men the best of care and treatment from all angles possible.

There are certain angles of military life that I wish to call to your attention that are of extreme importance. The foremost of these is that of military discipline. This subject is one but little understood outside of the Army and, it must be confessed, is not always viewed in its proper light even within the Army. It has been said that the trouble seems to be that most people either do not, or will not, grasp the proper meaning of what is called military discipline, its nature, its purpose, its necessity, and finally and most important of all, its spirit.

Living within an atmosphere of strict discipline from the cradle to the grave, most people fail to grasp its primary principles. As a matter of fact, the idea of rigid discipline surrounds us every moment of our lives. We can never escape it for an instant. Practically every experience through which we acquire knowledge is in the nature of a disciplinary correction inflicted upon us by some agency of nature or of civilization.

Outside of military circles the average man recognizes fully the necessity of discipline in his family, his business, his relations with his fellowmen, because he is familiar with the conditions which surround the rearing of a family or which must govern the relations of men in civilized intercourse.

On the other hand, he is not familiar with conditions in the military service; hence, he does not understand the reasons for the rules and regulations, and in consequence is more than likely to view them with intolerance. Even within military circles, among men who should be familiar with the reason and spirit of military regulations and military procedure, many make the serious mistake of confusing the exercise of authority with the maintenance of discipline. In brief, they appear to think that discipline must be maintained solely for the purpose of upholding their authority, and again, both outside and inside of military circles, many fail to understand the

* Read at the Symposium of Military Medicine, Boston meeting of the American College of Physicians, April 24, 1941.

spirit upon which true military discipline is based and must be based. Failing in this, they fail altogether, for the simple reason that men can understand the principle of military discipline only when they appreciate its underlying spirit.

Without the proper spirit there can be no such thing as discipline in any army. Proper discipline should in no sense be based upon the fear of disciplinary correction, since in this instance we merely have schoolroom discipline. The discipline upon which a successful army must be built is a different kind,—a kind that endures when every semblance of authority has vanished, when the leader has fallen, when members of the team are dropping out one by one and when the only driving power that remains is a strong and unconquerable spirit of attainment. *This concept gives us at once a working definition of military discipline, the spirit of the team.*

Strange as it may seem, an element of good discipline is the fear of losing the respect of one's fellow soldiers or officers, and this desire for esteem is one of the essentials of military discipline. It is to be seen in all trained and disciplined units the members of which feel for each other a natural respect and admiration. The knowledge that he enjoys the respect and admiration of his fellow soldiers is a source of the greatest pride to each member of the unit. The desire to retain this respect, to be looked upon as a worthy member of the unit, is greater than a man's fear of injury.

Oftentimes the question may be asked, "Of what necessity is military discipline?" I can only refer you to the necessity of team work in any undertaking, irrespective of whether it be team work in a set of doubles at tennis or the training of an Army of a million and a half soldiers.

In our present emergency we are attempting to inculcate in the minds of our soldiers the necessity of properly protecting our country in the event of attack. As Major General William A. Pew, Massachusetts National Guard, states in his manual, *Making a Soldier,* the kind of soldier who interests us is the one who finds satisfaction in serving a cause and who has learned to expend his energy for that cause. He must be physically developed, trained to conserve health, and he must perform with technical skill his part in every incident.

Besides these qualifications he must have the mental attitude of a soldier. To attain this proper attitude is an important step; there is an ideal which is characterized by the tendency to correct action and supreme satisfaction in such action.

In this short treatise, considerable stress is placed upon the process of acquiring proper military habits and the author gives four maxims:

1. Select the habit.
2. Demonstrate the habit.
3. Secure abundant and genuine practice, with every effort of will and attention directed toward acquiring the habit.
4. Allow no exceptions.

Under this grouping this author classifies military bearing, courtesy, putting forth physical and mental efforts (that is, high level of efforts), self control (physical and mental), neatness and order, smartness, exactness, and promptness; sub-conscious obedience, mental alertness, and confidence; and last but not least, team work in all military efforts.

In order to procure the best possible selectees to conform to the standards laid down by the Army, the Surgeon General's Office, in conjunction with the Selective Service System, has issued circular letters containing instructions to neuropsychiatrists examining selectees and recruits for the Service. In these circular letters the idea is again stressed that Army life is to be looked upon as a vocation and that certain types of individuals are adapted to this vocation and others are not.

No applicant is rejected unless we have definite neuropsychiatric evidence that he will be unsuitable material for training in the Army. It is further stressed that the soldier must be looked upon as a fighting unit, capable of adapting himself to the restrictions and inhibitions of personal desire and comfort, as well as to the deprivation of food, rest, shelter, and as occasion arises, to the extraordinary demands of prolonged physical and mental activity during active military service.

It has been further stressed that there are many individuals of abnormal personality traits who are capable of satisfactory adult adjustment in civilian life. For this class there are in civilian life numerous avenues of escape available, but such individuals will be a total loss when it comes to adjusting themselves to a pattern which is more or less inflexible and of necessity limited and circumscribed as to self-expression. When thrown upon their own meager resources of adaptation to Army environment, requiring contact with all kinds of personalities, some who are just able to adapt themselves to life under the most favorable conditions will not fit into that one iron mold which experience has taught is essential to military success.

Applicants who exhibit definite personality deviations are referred for special psychiatric survey and are rejected if they are considered as undesirable material for training. It is estimated that over 50 per cent of the present beneficiaries of the Veterans Bureau are individuals of this type who were accepted in the Army in 1917.

The Army is one of the elements of national defense, and its present mission is one of preparation for offensive and defensive warfare. It is, in no sense, a social service or a curative agency. It is to be considered neither a haven of rest for the wanderer or shiftless, nor a corrective school for the misfits, the ne'er-do-wells, the feeble-minded, or the chronic offender. Furthermore, it is neither a gymnasium for the training and development of the undernourished or underdeveloped, nor is it a psychiatric clinic for the proper adjustment of adults who need emotional development. Therefore, there is no place within the Army for the physical or mental weakling, the potential or present behavior problem. If an individual is a behavior problem in the

civilian community, he will certainly become a more intensified problem in the Service.

In our present training schedule, it must be forever kept before our minds that our soldiers are coming from all walks of life, from distant points of the country, from farm and factory, from ranch and bench,—the rich and the poor, the illiterate and the educated,—and all are thrown together into a heterogeneous mixture and subjected to the same discipline, the same regulations, the same dull routine.

The selectee coming from the average American home has received the fond care and protection of indulgent parents. He has been protected from all disturbing and disrupting influences that might interfere with his normal development. His parents have been interested to see that he had the proper clothing for all types of weather, that he did not leave the house without his overcoat, overshoes, muffler, or whatnot in inclement weather. New problems that confronted this individual were promptly taken over by his protectors and solved by them.

In other words, his entire life has been guarded and protected, and his course of action steered by over-seeing parents. His personal responsibilities have been at a minimum, and he has not been trained to accept life as it really is.

Upon this boy's induction into the Army, you will readily see that a tremendous amount of psychological readjustment must be made. Here he must train himself to stand upon his own feet, to make decisions, learn to live with other men, adapt his own personal wishes to the wishes of others about him. He must live in close contact with his fellow soldiers and adjust himself to their method of living.

In other words, he is passing from a set of circumstances where the stage was set about him and his wishes, to one where he must recognize, appreciate, and conform to the personal desires and wishes of his fellow soldiers.

This readjustment will have a wonderful effect upon the boy's future. During the recruit's first year of service, he will experience a well-planned period of training to develop his professional abilities as a soldier, as well as to develop his character.

After the selectee has been chosen, ordinarily he will be sent to one of our training areas for a period of 13 weeks' training. In the case of the Medical Department, the instruction day is assumed to be eight hours, more time per day being utilized when desirable, especially in connection with marches, field exercises, and the like. The open time will be used to compensate for interruptions, to bring units or individuals up to standard, or to provide refresher training.

During the first two weeks, the training of the enlisted man will be stressed. At the end of this period, he should be able to wear, display, and properly care for his uniform and equipment, to march, to pitch shelter tent, and to understand the essentials of the basic subjects prescribed in this program, such as:

Military courtesy and discipline
Military sanitation and first aid
Care of clothing and equipment
Individual defense against chemical warfare
Individual defense against air and mechanized attack
Interior guard and close order drills
Equipment, clothing, and tent pitching
Marches and bivouacs
Physical training, group games and mass athletics.

During the second period of training, from the third to the tenth week inclusive, stress is placed upon basic technical subjects which fit him for his place in the unit.

In addition to the basic subjects, specialized training and technical and logistical training are started.

Technical

Hasty entrenchments and shelter (camouflage)
Drill, motor carriers, and motor units
Motor vehicles, care, operation, and convoy
Map and aerial photograph reading
Movement by motor entrucking and detrucking
Movement by rail, entraining, and detraining
Loading and handling cargo

Medical Department Training

Elementary anatomy and physiology
Nomenclature and care of organization equipment
Field medical records
Treatment of gas casualties
Litter drill, including ambulance loading and unloading; and passage of obstacles
Field sanitation and sanitary appliances
Materia medica and pharmacy
Medical and surgical nursing
Heavy tent pitching
Organization and function of the arms
Organization and function of the medical unit
Medical aid (splints and splinting; bandages and dressings)

Tactical and Logistical

Scouting and patrolling, use of cover and concealment
Orientation in night combat
Communications in combat

Unit training (medical units)
Battalion tactical training
Regimental tactical training
Troop movements by motors
Inspections

The final period, from the tenth to the thirteenth week, inclusive, is known as the tactical period.

Function and combat dispositions of sections of headquarters and service, collecting, ambulance, or clearing elements
Reconnaissance, use of cover and concealment
Collection and evacuation of casualties from the field (day and night)
Ambulance driving shuttle (day and night)
Ambulance driving convoy (day and night)
Nursing and ward management
Transportation and supply requirements
Procurement and issue of supplies
Selection and occupation of various station sites, and the functioning of such stations
Forward displacements and withdrawals during action
Operation of regimental and battalion dispensaries
Battalion or regiment training.

It is astonishing how well and how rapidly recruits adapt themselves under these most difficult conditions. It is the duty of every officer to forever keep these conditions in the foreground and to lend every opportunity to advise and counsel with the men placed beneath him for proper training in military life.

Every effort has been made by the War Department to take proper care of the soldier from a medical and physical standpoint. The daily duties are properly coördinated to give him sufficient periods of rest and relaxation; he will be kept busy in mastering the new technic of his vocation. The activities of the various welfare associations have been adequately correlated and will be used to their fullest extent. A distinct effort has been made by the War Department to place the new soldier in the position for which he is best fitted; and every soldier is interviewed with this end in mind upon his entrance into the Service.

Recruits are encouraged to keep in contact with their family and friends by personal correspondence and by personal visits; they are given ample permission to leave the post in order to visit home and relatives when it does not interfere with their proper training schedule.

The entire program aims at producing an efficient, well-disciplined, high-morale Army that will satisfactorily protect our country in the event of necessity.

As one of our officers has expressed in his writings, the foundation stone of Americanism is uniform justice to all. This is what the enlisted man expects and this is what appeals to all. He is the finest soldier in the world; it is a great privilege to train him. Remember, he often comes from a home where there were few advantages and opportunities. Don't expect too much of him at first. He presents himself to be shown, to be instructed, to be molded properly, into this Army of ours. Have patience with him. Remember that many things which are an old story to us are new to him. Show him a thing clearly before you question him about it. If you are fair and square and interested in the general welfare of your men, you will appeal to them and they will follow your guidance willingly.

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SILENT OR ATYPICAL CORONARY OCCLUSION *

By WILLIAM D. STROUD, M.D., F.A.C.P., and JOSEPH A. WAGNER, M.D.,
Philadelphia, Pennsylvania

RECENT papers by Blumgart, et al.[1, 2] wherein careful correlation between clinical records and exacting pathological studies were carried out, have again drawn our attention to the extensive potential collateral circulation that exists in the myocardium and secondly to the fact that, "coronary occlusion, per se, does not necessarily produce any characteristic clinical manifestations." "If an occlusion occurs gradually, with concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable. Then what we speak of as 'coronary occlusion' which consists of substernal pain and oppression, a fall in blood pressure, pallor and typical electrocardiographic changes, fever, leukocytosis, etc. is in reality myocardial infarction."

TABLE I

A Few of the Many Clinico-Pathological Reports on Coronary Occlusion

	No. of Cases	Per Cent Without Pain
Morawitz and Hochrein [10]	91	75.0
Willius and Brown [11]	86	25.0
Nathanson [12]	113	20.0
Pollard and Harvill [13]	375	8.5
Kennedy [14]	96 (recent)	8.3
	102 (old)	36.3
Boyd and Werblow [7]	127	33.0
Gorham and Martin [15]	100	42.0
Stroud and Wagner	49	26.5

Many cardiologists have been conscious of this differentiation for some time. Smith [3] writes, "complete occlusion . . . may not be suspected during life" and that there may be "sclerosis of coronary arteries out of all proportion to clinical manifestations." Levy [4] who developed the "Anoxemia Test" for the detection of coronary artery disease recognized that "advanced disease of coronary arteries may be found at necropsy in persons who, during life, never experienced discomfort referable to the heart." It appears as a result of the writings of these authorities and others that "silent" coronary occlusion is a clinical and pathological fact. The explanation offered is that sufficient collateral circulation has developed to prevent acute anoxia and ultimate necrosis of localized areas of myocardium.

* Read at the Boston meeting of the American College of Physicians, April 22, 1941.

This work has been done through the Robinette Foundation of the University of Pennsylvania and the M. W. Stroud, Jr. Fellowship in Cardiology of the Pennsylvania Hospital.

Does " silent " or painless myocardial infarction occur? White [5] states that " if coronary obstruction and cardiac infarction develop slowly and there is no excessive cardiac strain, there may be no symptoms at all even though there be extensive areas of damaged muscle and even if one or both coronary arteries have been occluded." East, et al.,[6] Boyd and Werblow,[7] Wedd [8] and Wigser [9] have described cases of proved myocardial infarction whose only complaints were sudden dyspnea and progressive failure.

The literature includes many reports on the correlation of clinical and pathological findings in cases of coronary artery disease. The incidence of painless occlusion in these series appears quite high.

Unfortunately it is impossible in some of these reports to discern what is the exact pathology described, i.e., coronary sclerosis with narrowing of the lumen, coronary thrombosis with or without myocardial infarction or if infarction is present, whether or not it is old or recent. Further, unless very careful pathological examination is made by a pathologist especially trained

TABLE II

Acute Myocardial Infarction Without Pain

	Cases	Symptoms
Hypertensive	2	Vertigo and syncope
Arteriosclerotic with mild failure	7	Sudden increasing dyspnea and failure
No cardiac history	4	Sudden dyspnea; with pulmonary edema in one case

in cardiac pathology, it is very possible that a goodly number of coronary occlusions together with small myocardial infarcts would pass undetected.

Looking at the clinical side from a critical standpoint, one is concerned with the questions, who took the histories, with how much care and how completely are they recorded? By some, the vague discomforts described would be ignored and yet by others, especially trained, interpreted as typical angina pectoris. Often the patients are too sick to permit an exhaustive history and sometimes too deeply narcotized, especially postoperatively, to present a reliable record.

A review of our cases of acute myocardial infarction as proved by progressive serial electrocardiographic changes or by necropsy examination at the Pennsylvania and Bryn Mawr Hospitals for a limited period of time was undertaken. Cases suggestive but not proved by the above methods of examination were not included. It is to be remembered, however, that there are certain areas of cardiac infarction, especially along the lateral wall of the left ventricle, that are relatively " silent " so far as the electrocardiogram is concerned. Patterns for this area have recently been described. A resumé of our cases of painless myocardial infarction is summarized in table 2.

A few of the more typical cases are briefly described and their respective electrocardiograms presented.

Case Reports

Case 1. U. A., white female aged 49 years. No history of previous illness except slight dyspnea for three months. The patient was admitted to the hospital with a chief complaint of severe dyspnea with onset 48 hours previously. Examination revealed no pain, substernal or elsewhere but the patient was acutely ill with râles at both bases of the lungs and a blood pressure of systolic 170, diastolic 100. Gallop rhythm was present. A blood count revealed white blood cells 26,300. The following day her right foot became blue and cold with the pulses absent. Serial electrocardiograms showed a typical anterior infarct which permitted the diagnosis of mural thrombus with embolism to the right popliteal artery. Death ensued.

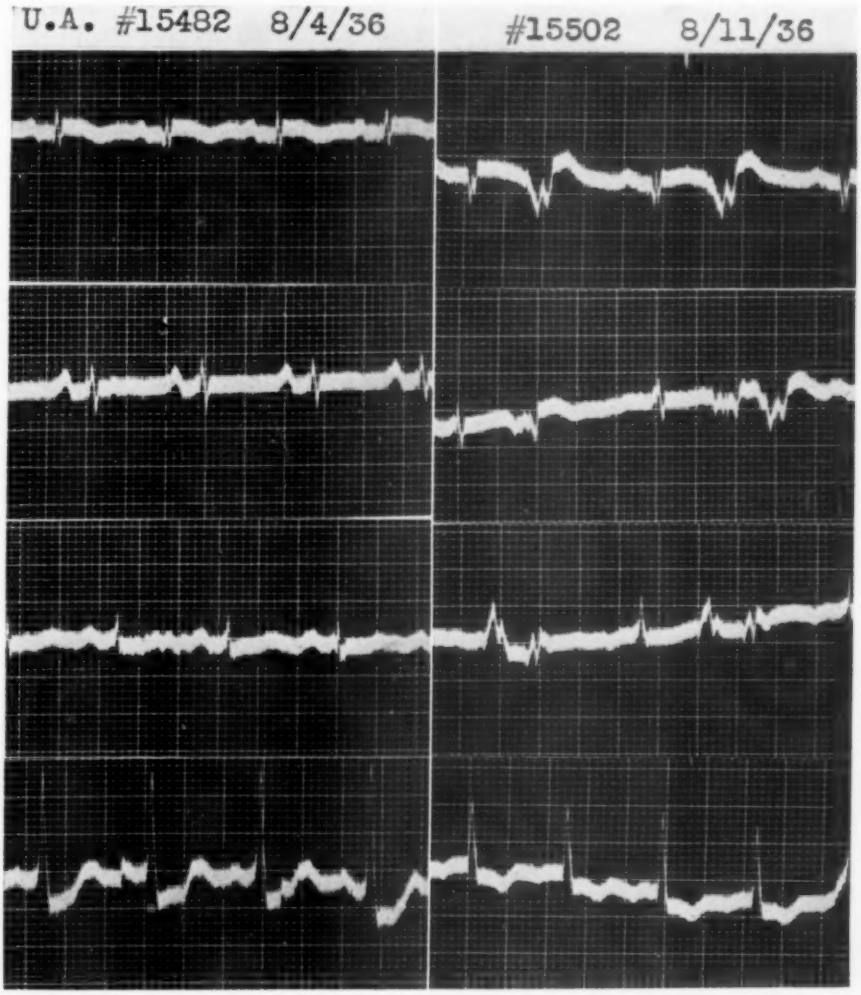

Fig. 1. U. A. Electrocardiograms of Aug. 4, 1936: Typical RST changes of acute infarction involving the anterior wall. Electrocardiograms of Aug. 11, 1936 show further changes confirming this condition.

Case 2. J. F. B., white male, aged 76 years, was known to have hypertension (blood pressure systolic 170, diastolic 110) and arteriosclerotic heart disease requiring digitalis. On March 23, 1941 the patient had much "gas" and belching but no pain. This continued through the night and the next day examination revealed a blood pressure of systolic 130, diastolic 82; temperature 100° F.; pulse 60; possibly slight congestive failure present. On March 25, 1941 a loud friction rub medial to the apex was audible. The white cell count was 18,300. Electrocardiograms showed an acute posterior myocardial infarct. Death ensued.

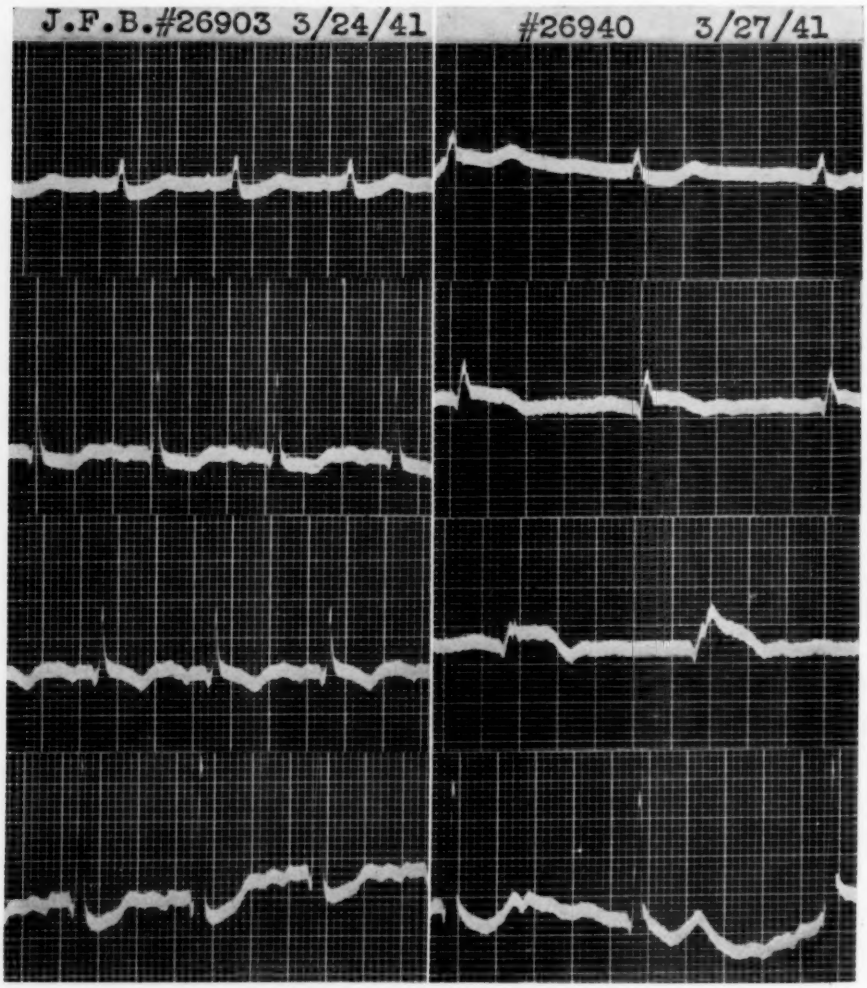

FIG. 2. J. F. B. Electrocardiograms of March 24, 1941 suggestive but not conclusive evidence of acute infarction of posterior wall. Electrocardiograms of March 27, 1941 show further evidence in support of this condition.

Case 3. H. T., white male, aged 51 years, with a history of hypertension. He collapsed on the street because of severe dyspnea but had no pain of any description. The patient was exceedingly orthopneic and pulmonary edema was present. Examination revealed that his heart was enlarged to the left with a ventricular rate of 120 and normal sinus rhythm; blood pressure systolic 130, diastolic 90; white blood cells 17,500. The diagnosis was left ventricular failure. Serial electrocardiograms showed a myocardial infarction.

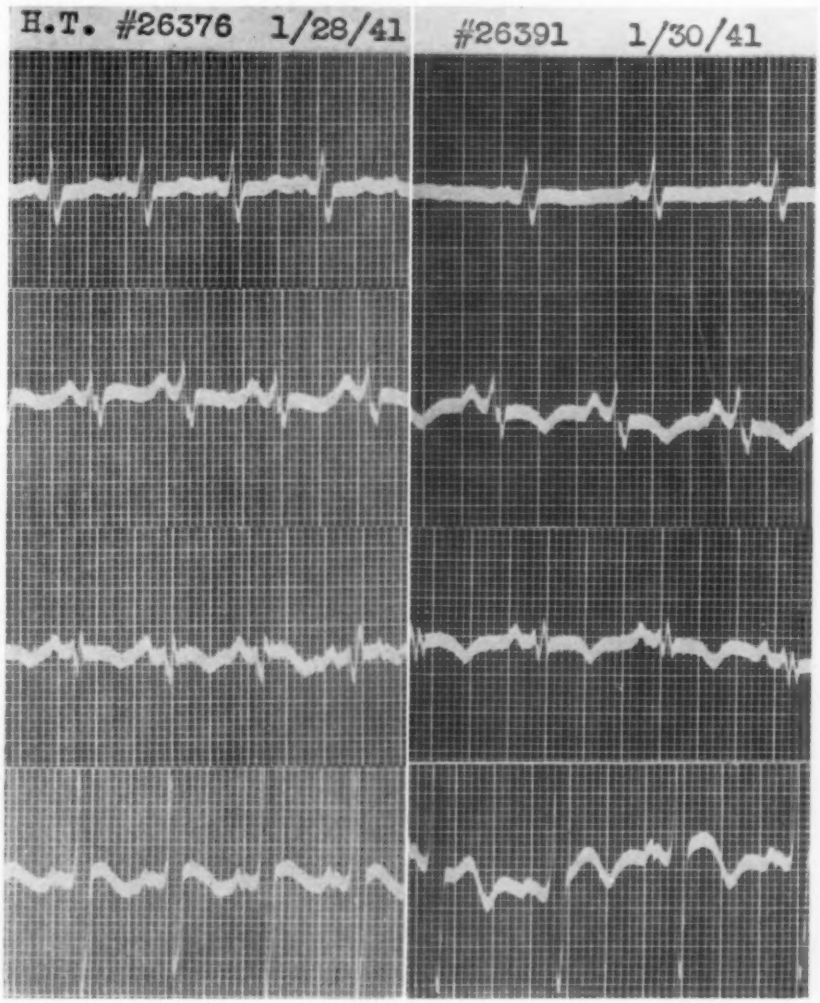

FIG. 3. H. T. Electrocardiograms of Jan. 28, 1941: Changes suggestive of myocardial infarction. Electrocardiograms of Jan. 30, 1941, show progressive changes which further confirm the original impression.

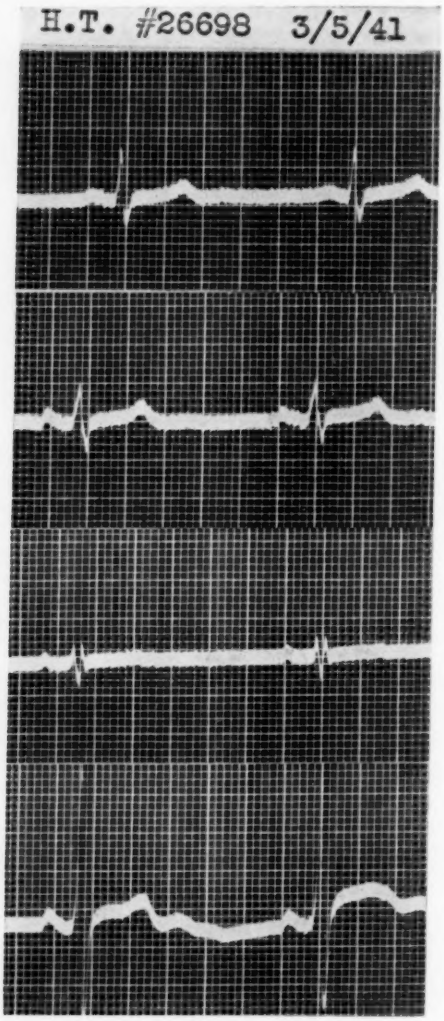

FIG. 4. H. T. Electrocardiograms of March 5, 1941 show further evidence of change; now nearly normal.

COMMENT

It is interesting to speculate on how painless coronary occlusion and painless myocardial infarction do occur. Most of us believe with Levy [4] and others that heart pain is the result of myocardial anoxia no matter how brought about. Coronary occlusion, we say, can be painless because of an established compensated collateral circulation, but this is not the case in myocardial infarction.

The explanation of painless infarction is difficult. Possibly the symptoms which they experience, such as swallowing, choking, gagging or dyspnea

may be pain equivalents. Possibly the nerve supply about the coronary vessels is different, or are they members of the hyposensitive group described by Libman?[16] Martin and Gorham[17] believe pain depends on coronary tension.

From a therapeutic standpoint, it seems to be extremely important to be cognizant of the possibility of coronary occlusion and myocardial infarction in the absence of pain. Vague symptoms of weakness, etc. in patients with hypertension or the onset of increased dyspnea, together with progressive failure in patients with previous mild failure, should make one alert to this serious condition. Putting the patient to bed and checking with serial electrocardiograms seem highly desirable.

The corollary may be equally true. Any patients with the typical pain of coronary insufficiency but no other suggestive clinical findings, even in the absence of changing T-waves in the electrocardiograms must be considered as possible cases of coronary occlusion without myocardial infarction and treated accordingly. This means total bed rest for a week or 10 days as a myocardial infarction might be developing. In these instances, clinical judgment is of much more importance than the electrocardiograms.

Summary

Painless coronary occlusion and myocardial infarction are discussed. A review of 49 cases of proved myocardial infarction, 13 without pain, is presented.

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THE EFFECT OF THIAMIN ON THE RESIDUAL NEURAL DISTURBANCES OF TREATED PERNICIOUS ANEMIA *

By J. C. ZILLHARDT, M.D., *Binghamton, N. Y.*, KEITH MACLEAN, M.D., *Vancouver, B. C.*, and WILLIAM P. MURPHY, M.D., *Boston, Massachusetts*

BY supplying sufficient amounts of anti-pernicious anemia substance it is possible to control the neural disturbances of uncomplicated Addisonian anemia. Certain residual neural manifestations are apt to remain, however, in spite of adequate liver therapy. This is particularly true in patients with advanced nervous system involvement and in those who have not been adequately treated at the onset.

Considerable thought has been given the various vitamins [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] in connection with pernicious anemia and its associated neural disturbances. At the blood clinic of the Peter Bent Brigham Hospital interest became focused on vitamin B_1 and studies were carried out in an attempt to determine what relationship, if any, the administration of this vitamin might have on remaining neurological manifestations of pernicious anemia that had been adequately treated over a period of time.

The term "adequate treatment" implies "that each patient receives an amount of potent substance sufficient to produce and maintain a normal state of blood in order to insure the maintenance of the best possible state of health . . . this may be accomplished by giving each patient exactly that amount of anti-pernicious anemia substance which will be in excess of that which is necessary to maintain a level of 5,000,000 red blood cells per cubic millimeter in practically all patients. In a few patients it may be impossible to maintain the blood at or above the 5,000,000 level, and it may be concluded, therefore, that provided that the blood is otherwise normal in every respect (and no complicating factors exist) a lower level is normal for them." [12]

All patients used in this study of the effect of vitamin B_1 on residual neural involvement of adequately treated pernicious anemia are represented by number in the accompanying table (table 1). In every instance neurological manifestations were present at the time the diagnosis of pernicious anemia was first made and in none had there been an aggravation of the neural complications once adequate liver therapy was instituted. On the contrary with such treatment all showed a striking initial improvement of the neural disturbances. This improvement eventually eased off to a more or less stationary level and there resulted certain neurological symptoms and

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From the Medical Clinic of the Peter Bent Brigham Hospital.

TABLE I

Case Number	Age	Sex	Duration of Maintenance Treatment in Years	Average Erythrocyte and Hemoglobin Levels			
				Before Vitamin Therapy		During Vitamin Therapy	
				Millions	Grams	Millions	Grams
1	62	M	3	5.48	15.80	5.38	14.63
2	56	M	14	5.48	15.32	5.08	15.46
3	67	F	8	5.09	14.08	5.06	14.49
4	65	M	6	4.70	15.40	4.66	14.63
5	74	M	5	4.85	16.28	4.85	16.28
6	48	M	5	5.15	16.42	5.44	16.97
7	46	F	14	5.48	15.73	5.48	15.73
8	56	F	7	5.36	14.49	5.23	15.18
9	67	F	6	4.45	12.97	4.55	13.52
10	70	F	1	4.69	12.97	4.27	12.83
11	60	F	5	5.72	14.63	5.60	14.63
12	72	F	4	4.78	13.52	4.55	13.66
13	71	M	4	4.79	12.28	4.98	13.39
14	74	M	5	4.66	15.04	4.52	14.49
15	49	F	1	5.47	14.21	5.47	14.21
16	78	M	2	4.65	13.80	4.56	13.59
17	62	F	½	4.56	14.21	5.46	15.87
18	58	F	½	4.56	14.40	5.81	15.46
19	66	M	7	4.92	14.63	4.75	14.77

3 c. c. Conc. Sol. Liver Ext. (Lederle) intramuscularly was used in the treatment of all above patients.

signs that neither improved nor became aggravated as adequate liver therapy was maintained.

What improvement in neural manifestations other than that, which they had already made, is possible in patients such as these in view of the probable pathological lesion in the nervous system? The neurological signs and symptoms of pernicious anemia are believed by various workers to be essentially due to:

1. Such dysfunction of the end organs of the peripheral nerves as is supposed to occur in cases of severe anemia.[13]

2. Degenerative changes in the peripheral nerves [13, 14, 15, 16, 17, 18, 19] that may be due to the anoxia of marked anemia [13, 15, 16] or in some cases to a food factor deficiency [20] or both.

3. Edema of the cord associated with degenerative processes in the white matter.[17] In some acute cases this edema is believed to be marked and to be responsible for considerable neural disturbances.[13]

4. Degenerative changes in the tracts of the spinal cord particularly those of the posterior and lateral columns.

5. Structural changes within the brain.

Keeping in mind the length of time that our subjects had been receiving adequate treatment it seemed quite probable that no manifestations were present as the result of anemia per se or as one might find in acute cases, also that whatever lesions existed in the central nervous system were quite permanent and irreversible.

The chances then of doing more for these patients lay in:

1. Prevention of any progression of the neural complications. This was being taken care of by adequate liver treatment.[12]
2. Possibly in some way increasing the efficiency of the undamaged portions of the neural mechanism.
3. Attempting cure of any reversible structural changes that might still be present in the peripheral nerves.
4. Further improving the patients' well-being thereby possibly bettering neurological function.

It might be well to mention here that in so far as could be determined, all of our patients had been on adequate diets since their first attendance at the blood clinic, and with scarcely an exception none was known to have had any serious dietary abnormality before. The possibility, however, of a misleading history or improper absorption or poor utilization of some food factor was kept in mind.

All the above aspects were carefully considered before the study was begun. It seemed that any therapy, that would possibly be conducive to some further improvement in such cases as these, was worth while.

The individuals under discussion had probably attained the maximal effect that liver therapy alone could produce particularly in so far as the neurological disturbances were concerned. With this as a hypothesis it seemed reasonable to assume that, if a new therapeutic agent was added to the therapy already being instituted, whatever further improvement should occur must be related to the physical or psychological action of the new therapeutic agent.

At the time the study was started, as has been mentioned, all subjects had been receiving adequate pernicious anemia therapy. This therapy was continued just as it had been in the past. In addition, patients 1 to 7 inclusive were given thiamin * 1 c.c. intramuscularly three times per week for four months. The preparation used contained 10 milligrams or 3,000 international units of thiamin (crystalline vitamin B_1) per cubic centimeter. Patients 8 to 14 inclusive were given 3 mg. of thiamin * twice a day by mouth for four months. Each milligram of this preparation contained 330 international units. Patients 15 to 19 inclusive acted as controls. They were given 1 c.c. of normal saline intramuscularly three times per week in addition to the liver treatment.

Due regard was given to the possible psychological effects of this treatment and every effort was made to guard against them. To all patients including the controls it was explained at the start that in addition to the liver treatment which they were receiving, they were to be given a new therapeutic agent that might or might not bring about further improvement. The physician took care not to show any enthusiasm in regard to the new medicine or

* Furnished by Lederle Laboratories, Inc.

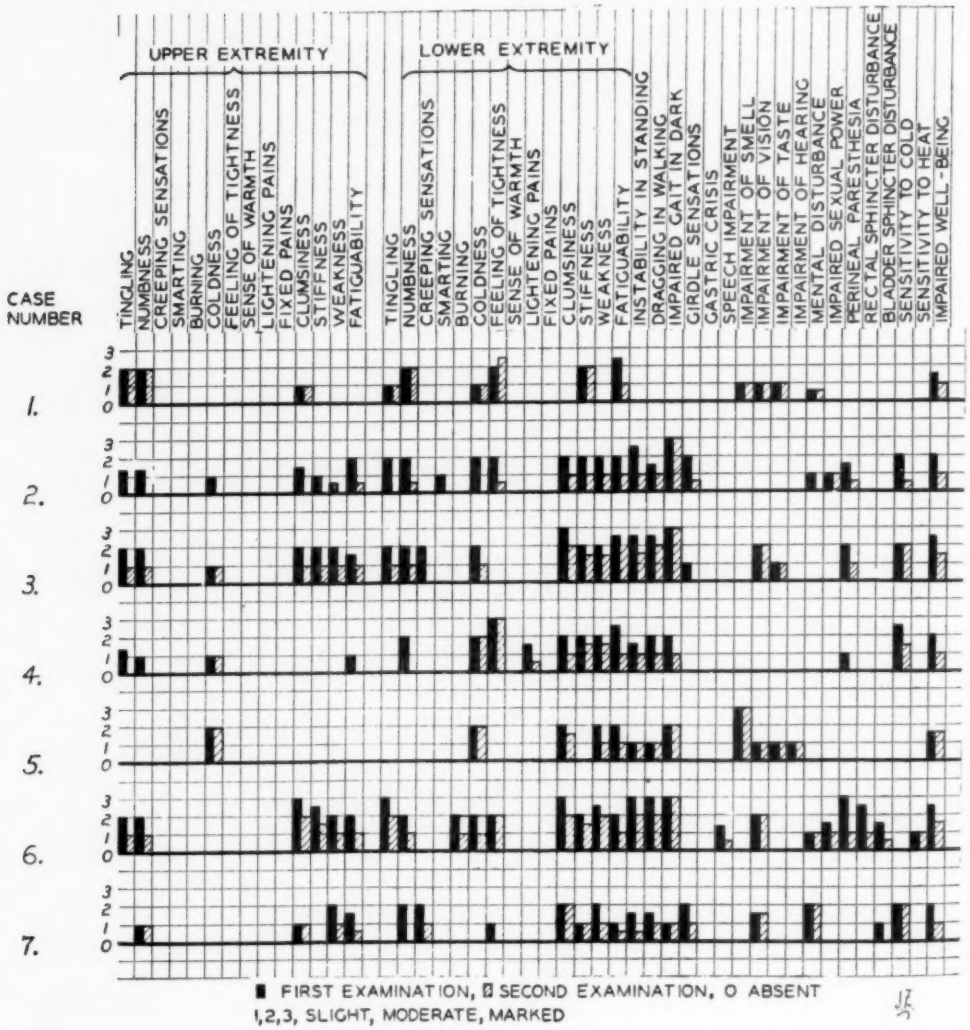

FIG. 1.

in any way unduly raise the patient's hopes. Effort was made to give each patient approximately the same amount of attention at each office visit.

All subjects had had physical examinations from time to time at the outdoor clinic. Also many had had careful study as patients in the hospital. The neurological portion of the more recent of these examinations checked favorably with our initial findings. In our study the neurological examinations were performed by two physicians and were carried out partly or completely in duplicate as the individual case warranted. The examinations necessarily were quite lengthy. If it were felt that the subject was becoming unduly fatigued, he was allowed to go home and the examination was com-

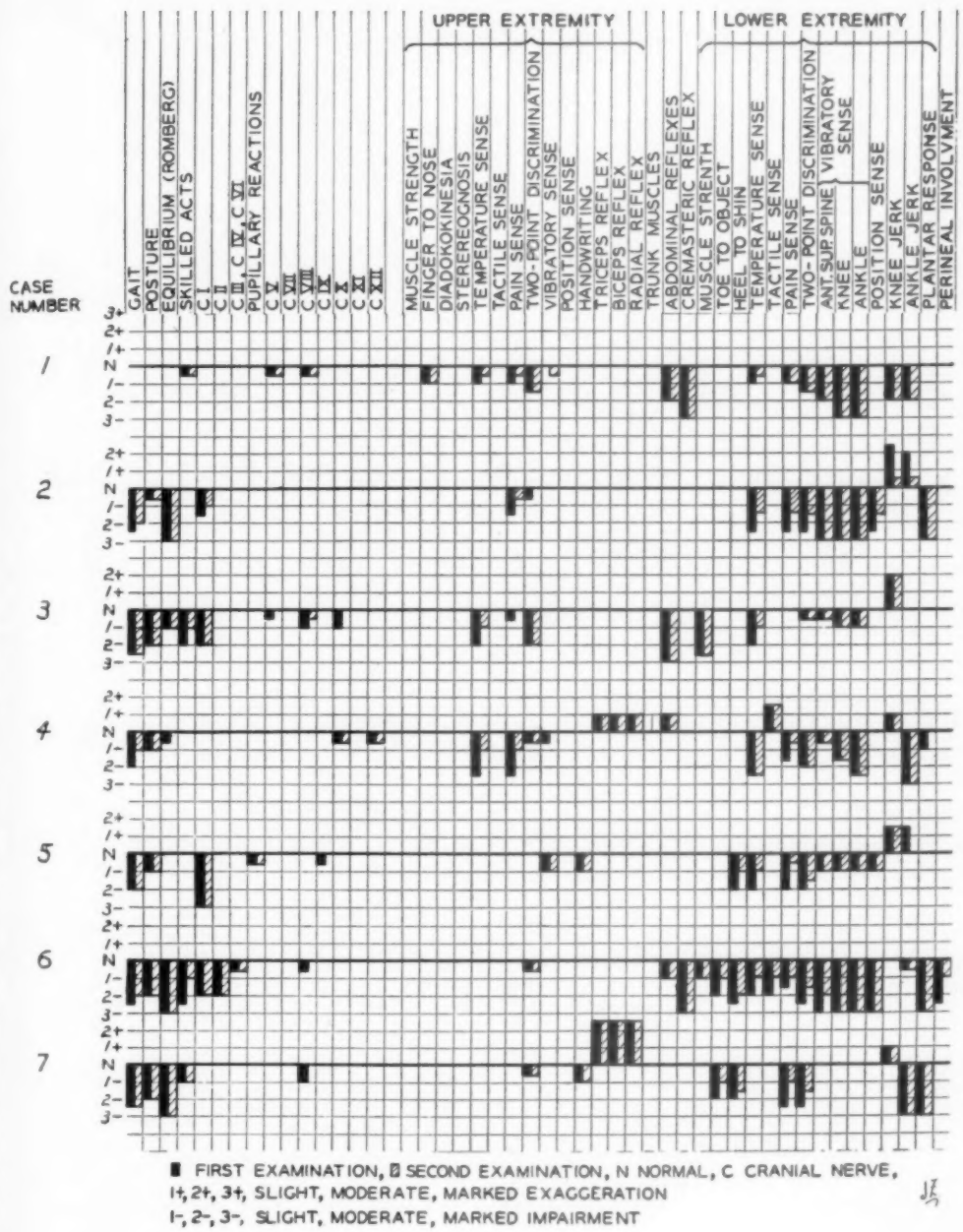

FIG. 2.

pleted at a subsequent visit. Each of the 19 individuals was examined when treatment was first begun. They were examined a second time at the end of two months and a third time two months later. That is each patient received three examinations during the four month period of treatment.

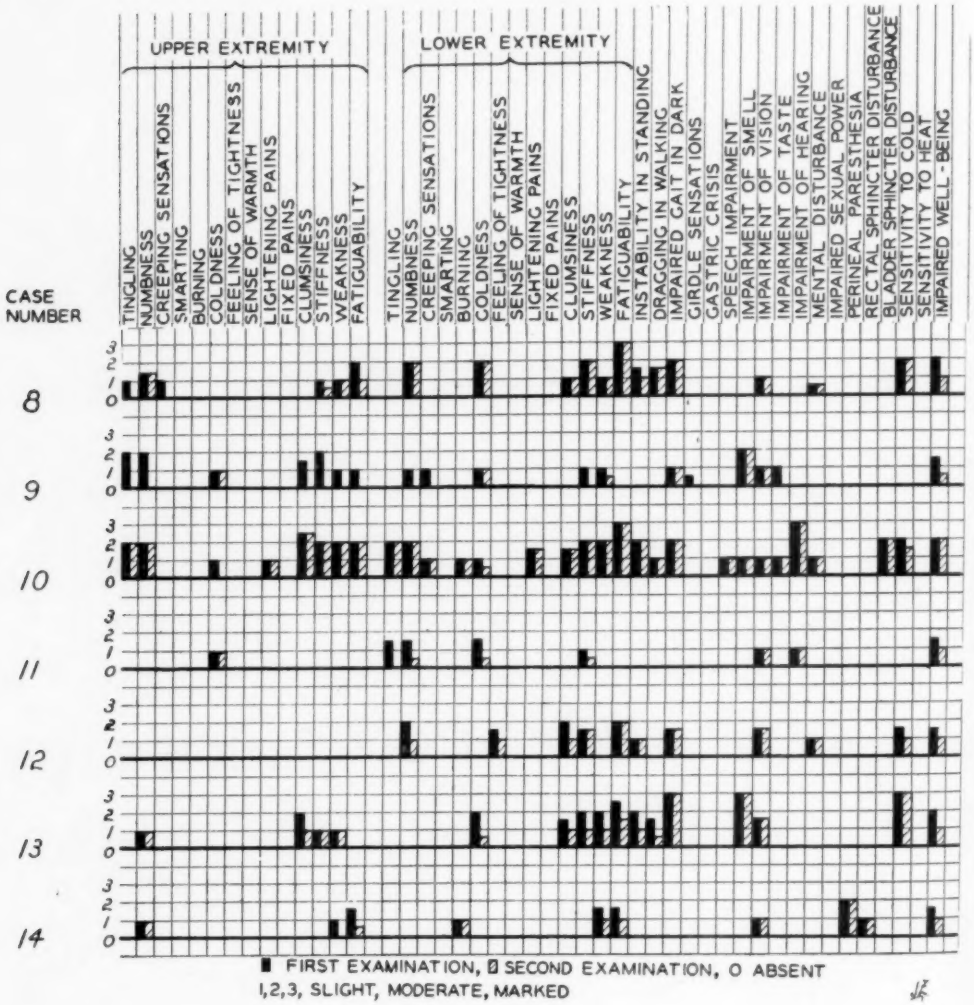

FIG. 3.

One very interesting observation was the fact that in all of the 19 cases there was little or no difference in the findings of the last examination as compared with the second. In other words it seemed that whatever changes occurred during the four month period of treatment were present at the end of the first two months. Little, if any, variation of symptoms or signs seemed to occur during the second two month period. Because of the similarity of the findings of the second and third examinations, the latter was omitted from the accompanying figures.

Figure 1 illustrates the subjective findings of those patients who received thiamin intramuscularly. With the exception of individuals 1 and 5 all experienced symptomatic improvement with treatment. Numbness and ting-

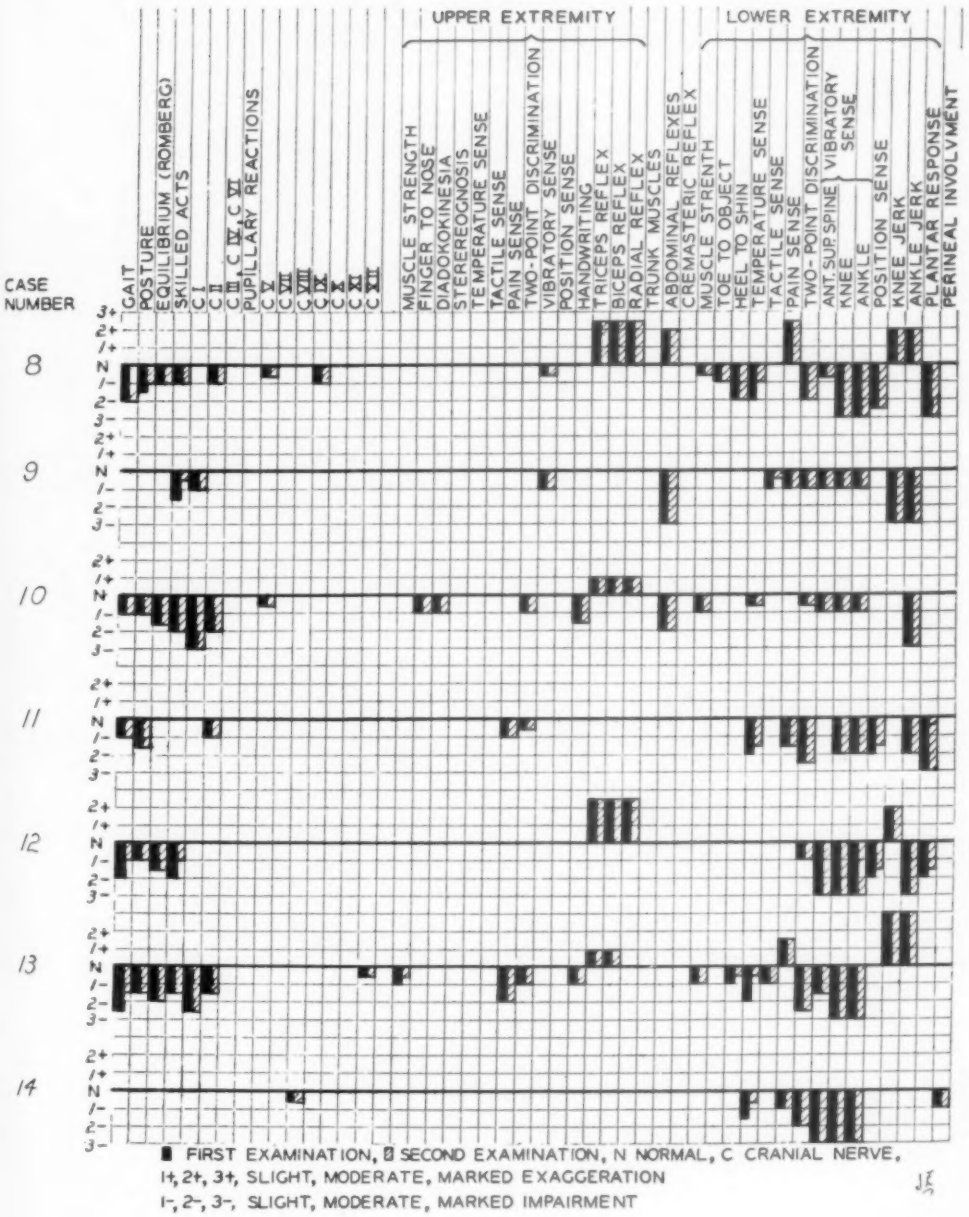

FIG. 4.

ling were diminished as was burning, when this was present. Those who were troubled with clumsiness, stiffness, weakness or fatigability of the extremities were convinced that these symptoms became less marked. There was likewise improvement in equilibrium. No change in the special senses occurred where these were involved. Improvement in perineal paresthesia

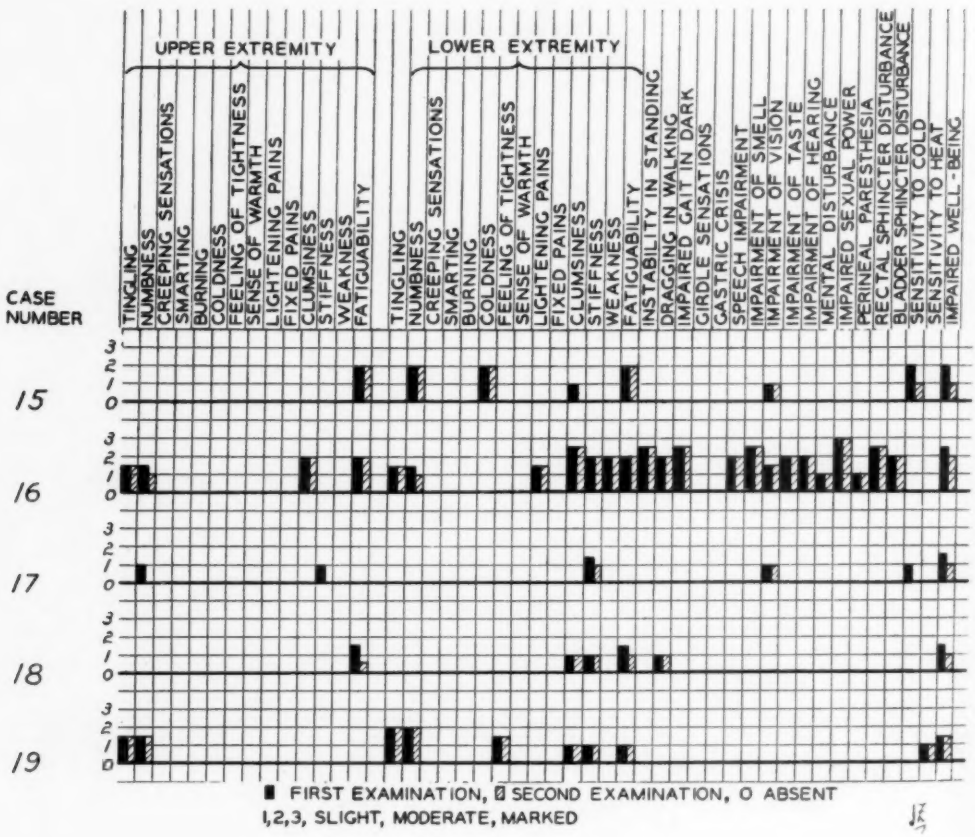

FIG. 5.

was noted in individuals 2, 3, 4 and 6. One patient, 6, who was insensible to movement of the bowels felt that this difficulty greatly subsided. Sensitivity to cold became less marked in two instances.

It will be seen from figure 2 that the principal improvements found on physical examination were in temperature sense, pain sense and in two point discrimination. The toe to object test and heel to shin test were carried out more accurately in a few instances. Patient 6 had considerable perineal anesthesia that became less marked after treatment. This man also seemed to show some improvement in vibratory sense over the anterior superior iliac spines, as determined with a calibrated tuning fork. In patient 4 an abnormal plantar response was present on first examination. Some improvement in position sense of the toes was found in individual 2. This man had considerable exaggeration of the knee and ankle jerks on first examination. Patellar clonus was elicited at that time. These reflexes gradually improved to the point where they were considered but slightly hyperactive.

Figures 3 and 4 show the results of the examinations of those who were

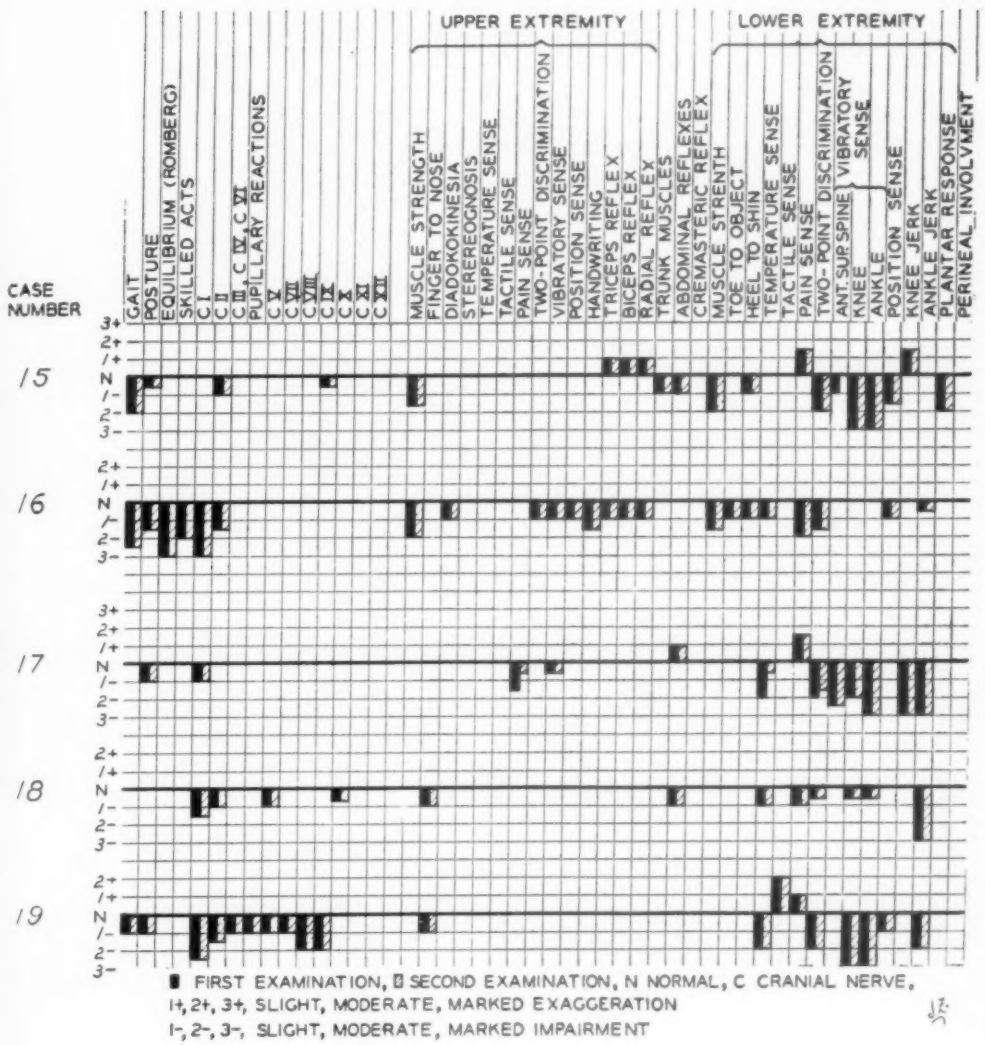

FIG. 6.

given thiamin by mouth. With the exception of improvement in well-being it will be noted that little change occurred during the period of therapy.

Figure 5 indicates the symptoms and figure 6 the signs of those pernicious anemia patients who acted as controls. This is the group that was given normal saline intramuscularly three times per week. At the time of the second examination all of these individuals stated that they felt better in general, yet on further questioning there was little or no change in any of the individual subjective items as shown in the figure. It can also be seen that with the exception of patient 17 no objective changes occurred as result

of treatment. It is interesting to note that patient 17 showed improvement in pain sense, temperature sense and two point discrimination.

One has to be cautious in drawing conclusions from a study of this kind. Attempting to quantitate neurological symptoms and signs is a task that is subject to error under the most ideal circumstances. The intelligence and coöperation of the patient, as well as the judgment and patience of the physician are important factors. The element of disposition and of physical and mental fatigue on the part of both patient and examiner as well as the inaccuracy of existing procedures of examination come into play. The many possible variables are only too familiar to those who have occasion to do neurological studies. It is therefore with some reserve that an attempt is made to interpret our findings.

The administration of thiamin intramuscularly seemed to have some therapeutic effect in most of the patients who received it. Possibly in a larger series of cases, however, the results would not be so favorable. Yet it is conceivable that with such treatment the efficiency of undamaged neural tissue might become increased or existing reversible peripheral neuritic changes might become improved, or as a result of possible improvement of the patient's general health, neural function might become enhanced.

It is difficult to explain why the giving of thiamin by mouth was not as effective as when it was given intramuscularly. Those patients who took the medication orally were considered dependable. They were selected with this particular point in mind, yet it is possible that they did not give their full coöperation. The possibility of improper absorption or poor utilization of thiamin as given by mouth must be considered.

Summary

1. Our results suggest that the administration of thiamin might have a beneficial effect on those residual neural signs and symptoms of pernicious anemia that seemed stationary in spite of persistent, intensive anti-pernicious anemia therapy.

2. Our study would indicate that 3,000 international units of thiamin intramuscularly three times per week is more effective than 990 international units of thiamin by mouth twice a day.

3. In those instances in which neurological improvement took place the maximal beneficial effect occurred during the first two months of treatment. Continued use of thiamin after this period seemed to produce no further change.

4. The many variables that are involved in attempting to quantitate neurological symptoms and signs were carefully considered in this study.

We are very grateful to Miss Isabel Howard for her most valuable laboratory assistance.

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THE EFFECT OF A VITAMIN B COMPLEX ON THE RESIDUAL NEURAL DISTURBANCES OF TREATED PERNICIOUS ANEMIA *

By J. C. ZILLHARDT, *Binghamton, N. Y.*, ISABEL HOWARD, and WILLIAM P. MURPHY, *Boston, Massachusetts*

UPON completion of the study of the effect of thiamin on the residual neural disturbances of treated pernicious anemia the experiment was repeated under the same conditions using a vitamin B complex. A group of 13 patients was used in this work. As with the individuals treated in the aforementioned study, neurological manifestations were present at the time the diagnosis of pernicious anemia was first made. With adequate liver therapy there was improvement of the neural disturbances. This improvement had tapered off to a more or less stationary level and there remained neural signs and symptoms that neither improved nor became aggravated as adequate liver treatment was maintained.

Seven of this group were given 1 c.c. of a vitamin B complex † intramuscularly three times per week for three months in addition to continued adequate liver therapy. Each cubic centimeter of this preparation contained thiamin (crystalline B_1) 2 mg. or 600 international units, riboflavin (B_2) 0.3 mg. or 100 Bourquin-Sherman rat growth units, nicotinic acid 10 mg., dermatitis factor (B_6) 30 "rat day" units, filtrate factors approximately 30 "chicken growth" units. The other six patients acted as controls. They were given 1 c.c. of normal saline intramuscularly three times per week. Again adequate pernicious anemia therapy was maintained in each instance.

Neurological examinations were carried out in the same manner and at the same intervals as described in the previous study. At the end of the course of treatment an analysis of the examinations showed that with the exception of some improvement in well being the group that received the vitamin B complex showed little change in subjective and objective signs in comparison with the control group.

* Received for publication March 30, 1940.
From the Medical Clinic of the Peter Bent Brigham Hospital.
† Furnished by Lederle Laboratories, Inc.

THE SYNDROME OF MULTIPLE VITAMIN DEFICIENCY *

By V. P. Sydenstricker, M.D., F.A.C.P., *Augusta, Georgia*

Good nutrition depends not only on the intake of sufficient amounts of all the substances required for normal metabolic processes but also on their adequate absorption, storage and utilization. In the case of most of the vitamins it is probable that optimal intake varies with the demands of the body for energy production, repair or growth. The requirements for some members of the B group are definitely dependent on the composition of the diet and it is likely that there are interrelations or synergistic reactions between vitamins which further condition the requirements.[1, 2, 3, 4]

The development of avitaminosis is due to the failure or perversion of normal biochemical reactions which can be completed only when adequate supplies of vitamins are available. The functions of the water soluble and fat soluble vitamins seem to be very different. The B group of vitamins is necessary for the derivation of energy from carbohydrate and riboflavin may also be concerned in the utilization of fat [5] and in cellular respiration in the absence of haem. Ascorbic acid is thought to be important in various oxidation-reduction processes of cells and, in addition, is necessary for the formation of the intercellular cement-substance in all tissues. The fat soluble vitamins A, D, E and K seem to be requisite for the maintenance and repair of certain specialized tissues and the production of various physiologically indispensable substances. The water soluble vitamins as a group are rapidly absorbed to the point of saturation or of the limitations of storage, after which additional amounts ingested are excreted in the urine. It is likely that storage is never great because depletion can be brought about relatively quickly. The fat soluble group seems to be absorbed slowly but stored in considerable amounts so that depletion is seldom acute. An exception is vitamin K which is absorbed and utilized quite rapidly in the presence of adequate amounts of bile and which can be depleted very quickly when bile is absent from the duodenum.

Ever since the recognition of the classic deficiency diseases it has been customary to regard them as specific clinical and etiologic entities though variations in the pattern of each one have been noted by innumerable observers. When pure synthetic vitamins became available it was found that appropriate therapy with a single vitamin usually produced rapid and complete cure of the major manifestations of each of the avitaminoses but that certain other symptoms or signs might persist or grow worse.[6, 7, 8] Often

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such residual phenomena were referable to known vitamin deficiencies and responded to specific treatment, but their presence confirmed the suggestion by earlier observers that more than one factor might be concerned in the production of a typical deficiency syndrome.[9, 10, 11] Recent observations on the effect of deprivation of a single vitamin in normal human subjects maintained on carefully controlled diets have shown that it is quite difficult to produce the syndromes of pellagra,[12, 13] beri-beri [14, 15, 16] and scurvy [17, 18] by this means. Such results are not surprising since consideration of the background of spontaneous avitaminosis shows that depletion occurs either from very prolonged partial deficiency of intake or absorption of many vitamins or from great increase in requirements often in the presence of sudden and sometimes complete failure of intake or absorption.

It is traditional and correct to relate the incidence of vitamin deficiency to inadequate or unbalanced diet. Wherever endemic avitaminosis occurs, whether the prevailing pattern be that of pellagra, ariboflavinosis, beri-beri, scurvy or xerophthalmia, it is found that the food habits of the population result in the widespread use of excessive amounts of refined carbohydrates, suboptimal quantities of fat and quite deficient protein. Along with this goes minimal consumption of protective foods. Local custom may be very important in determining the clinical manifestations of endemic deficiency. The choice of hominy grits or of rice seems to determine the prevalence of pellagra or of beri-beri. Where collards replace cabbage as the staple greenstuff of the poor, evidences of vitamin A deficiency are distinctly rare.[19] Similarly deficient diets are often the result of individual choice or of physicians' instructions among persons not influenced by local custom and not subject to economic stress; dietary vagaries and poorly planned regimens for the treatment of peptic ulcer, heart disease or nephritis are frequent examples. It is obvious that the effect of a high-carbohydrate vitamin-poor diet is twofold: it not only fails to supply adequate amounts of all vitamins but actually increases the requirement for the B group.

The use of an unbalanced diet seldom or never results in acute or solitary avitaminosis since no naturally selected combination of foods is apt to be completely lacking in a single vitamin. It seems likely that prolonged partial deficiency produces functional and organic changes in the digestive tract which interfere with the absorption and utilization of the small amounts of vitamins available so that eventually a critical level is reached. The acute and often apparently uncomplicated manifestations of avitaminosis are apt to result from sudden large requirements for vitamins produced by the substitution of alcohol for food, maintenance on dextrose or severe febrile disease.

The relation of gastrointestinal disturbances and diseases of the liver and bile ducts to vitamin deficiencies has been stressed by many observers.[20, 21, 22] Anorexia resulting from organic disease of any part of the digestive tract diminishes food intake and is particularly apt to result in poor consumption of meats and vegetables. Present knowledge would in-

dicate that gastric achlorhydria interferes with the extraction of the entire water-soluble group of vitamins from food and that biliary obstruction with lack of bile in the upper bowel prevents adequate absorption of the fat soluble group. Gastric achlorhydria is common in all the avitaminoses and may be a result of chronically deficient diet as well as a factor contributing to disease.[23] Vomiting and diarrhea have long been recognized as causes of partial loss of ingested vitamins and edema of the gastrointestinal tract from any cause can prevent absorption. Diseases of the liver including fatty infiltration and chronic passive congestion prevent the cleavage of carotene into vitamin A, the synthesis of prothrombin in the presence of vitamin K and the adequate storage of all the known vitamins. Hepatic disease also may interfere with the utilization of thiamin, nicotinic acid and other members of the B group by retarding or preventing the formation of their physiologically active compounds. It seems quite certain that such intrinsic disorders are as unlikely to produce an uncomplicated avitaminosis as is faulty diet.

Interpretation of the clinical manifestations of a specific vitamin deficiency is based on evidence which frequently is incomplete. Accurate information can be obtained only by maintaining normal human subjects on diets so constructed and supplemented as to be deficient only in the substance under investigation. This is a formidable and frequently impossible task and such experiments are necessarily relatively brief. The effect of partial deficiency persisting for years rather than weeks or months cannot be expected, nevertheless much important information has been gained by this method. Hecht and Mandelbaum [24] were able to demonstrate that the earliest sign of vitamin A deficiency is delay in dark adaptation. Sebrell and Butler [12, 13] separated the syndrome of ariboflavinosis from pellagra and also showed that typical pellagrous dermatitis resulted from nicotinic acid deficiency. Williams and his collaborators [15, 16] and Jolliffe and others [14] have identified certain symptoms and signs of thiamin deficiency and Lund and Crandon and Dill [17, 18] were able to prove that some of the manifestations of scurvy can be produced by relatively short periods of ascorbic acid deprivation. Most of the criteria by which we identify specific deficiencies are derived from much less certain methods. The usual procedure is to maintain patients with frank deficiency disease on a grossly inadequate diet of known composition and to add vitamins seriatim, observing the effects of treatment. Even less satisfactory is the administration of a single vitamin to persons with multiple deficiencies. It is often impossible to evaluate results with either regimen because increased food intake from improved appetite may follow administration of any of the water soluble vitamins and particularly because we know little or nothing of the synergistic action of vitamins.

Brief consideration of the symptomatology of deficiency disease reveals the complexity of clinical pictures which result from deficiency of several vitamins usually at different levels of depletion. Weakness, nervous irritability, vague malaise, lassitude, muscle pains, anorexia and disturbances of gastrointestinal motility have been described as early manifestations of

vitamin A deficiency, beri-beri, pellagra, rickets and scurvy. They have been shown to occur in uncomplicated experimental thiamin deficiency [14, 15, 16] and probably reflect the metabolic defect of this avitaminosis at an early or physiologic stage. Photophobia, irritation of the eyes, blurring of vision, rapid visual fatigue, poor vision in dim light and night blindness are well recognized symptoms of vitamin A deficiency. Night blindness is specific, and delayed dark adaptation has been proved the earliest sign of avitaminosis A [24] but the other symptoms are frequent in pellagra and beri-beri where they are due to a complicating riboflavin deficiency. Mental confusion, forgetfulness, confabulation, depression, psychosis and stupor are common in pellagra and not infrequent in beri-beri. Often they occur in the absence of any physical sign of either disease. Frequently the rapid cure of such mental symptoms with nicotinic acid indicates that they are evidence of disturbed nutrition of cerebral neurones resulting from nicotinic acid deficiency.[25, 26, 27] Nervous and neuro-muscular symptoms very similar to those attributed to mild grades of thiamin and nicotinic acid deficiency but responding to neither have been relieved promptly by vitamin B_6.[28, 29]

In appraising the presenting physical signs of vitamin deficiency in any given case it is necessary to follow rather arbitrary criteria derived from clinical as well as experimental observation. Signs generally associated with thiamin deficiency are tenderness of nerves and of the calf muscles, hyperreflexia and hyporeflexia, muscular weakness and edema. Later, sensory disturbances and actual loss of motor function with or without cardiac manifestations are found. Not infrequently edema and tachycardia followed by other signs of heart failure dominate the picture. This is not the place to discuss the question of the specificity of all these signs [16, 30] since no better etiology has been offered. The diagnosis of nicotinic acid deficiency requires the presence of characteristic symmetrical dermatitis, of glossitis with atrophy of the lingual papillae, of lesions of the buccal mucosa or genitalia. With these there is almost invariably some part of the picture of mental disturbance already noted. The syndrome of ariboflavinosis presents cheilosis, glossitis, various grades of superficial vascularizing keratitis and seborrheic lesions of various sorts. The diagnosis of scurvy is made on the occurrence of gingivitis, hemorrhages into the mucous membranes, skin and tissues in general and, theoretically, a plasma ascorbic acid level of zero. Vitamin A deficiency is recognized by follicular keratosis or xerosis of the skin and cornea, delayed dark adaptation and low values for vitamin A and carotinoids in the blood. Evidence of lack of vitamin D in the adult is based on radiographic signs of loss of calcium from the bones and on abnormal phosphatase values in the blood.

It is notable that in clinical experience few patients present all the signs attributed to any single avitaminosis but that almost every one when examined with care shows those of several.

Certain patterns are much more common than others and these are mainly multiple B group deficiencies. Classical pellagra quite regularly presents the

cheilosis and corneal vascularization of ariboflavinosis and the muscle tenderness and reflex disturbances of thiamin deficiency. Less often there is edema due neither to protein deficiency, nor actual peripheral neuritis. Patients with frank beri-beri of either the wet or dry type seldom fail to show either the skin lesions or the glossitis of nicotinic acid deficiency and often there is cheilosis and the eye signs of ariboflavinosis. These combinations are of course to be expected from the nature of the etiology of B group deficiency. Rarely individuals with one of these syndromes has signs of vitamin A deficiency as well. This association is unusual in our locality. An occasional example is seen of an apparently acute phase of multiple avitaminosis which has been described as common in the tropics [31, 32] but which is rare in this country. This syndrome consists of severe ocular lesions and cheilosis similar to those of ariboflavinosis; ulcerative and atrophic glossitis, ulcerative dermatitis of the genitalia and vesicular dermatitis of the trunk and extremities such as are seen in severe nicotinic acid deficiency; follicular keratosis and a neuropathy of the optic nerve with swelling and congestion and marked dimness of vision. Such individuals have been too ill for experimentation but the very prompt cure of all lesions except follicular keratosis with large amounts of synthetic thiamin, nicotinic acid and riboflavin would seem to indicate that lack of these vitamins is the main fault. It is impossible to identify the factor responsible for the optic neuropathy with marked impairment of visual acuity and contraction of color fields. In our experience scurvy in adult patients is frequently associated with glossitis, ocular signs, dermatitis or reflex changes characteristic of deficiency of one or another member of the B group. What seems of more significance is that we have not seen a patient with clinical scurvy who had plasma ascorbic acid below 0.15 milligram per cent. It is likely that the associated B group and perhaps vitamin A deficiency play an important part in the development of scorbutic lesions.[19]

Though absolute proof cannot be presented, both clinical observation and therapeutic tests indicate that the presence of signs of any of the avitaminoses is indicative of multiple deficiency. In the case of the B group, treatment with the single vitamin indicated by predominant signs may result in the rapid development of severe manifestations of other deficiencies. In the majority of instances signs of multiple deficiency can be found without difficulty.

It is trite but necessary to say that a high protein, high caloric diet containing adequate amounts of the protective foods is the basis of all treatment of deficiency disease. The components of such a diet can be varied to suit the needs of the given case. Frequently it must be liquid and given in small amounts at frequent intervals through an indwelling nasal tube for several days. Such a diet should be supplemented with yeast or crude liver extracts and relatively huge amounts of the particular vitamin which seems to be predominantly lacking. In addition all other available vitamins should be given in amounts representing at least four or five times the normal daily requirement. In the case of the water-soluble group such massive dosage

is seldom required for more than a week though response may sometimes be quite slow in patients with beri-beri or very chronic ariboflavinosis. Delayed response can be attributed to some intrinsic disturbance which interferes with absorption or utilization. When no definite effect is observed after three days of intensive therapy by mouth it is advisable to change to a parenteral route. Thiamin and riboflavin frequently produce almost immediate effects when given intramuscularly or intravenously after failure on peroral administration. It may be wise always to give these vitamins by injection to patients who are urgently ill. The saving of time and material more than outweighs the increased cost of injectable preparations.

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GLUCOSE–SULFAPYRIDINE; EXPERIMENTAL AND CLINICAL STUDIES *

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When satisfactory oral therapy with sulfapyridine is impossible, or when it is desired rapidly to obtain high blood concentrations of the drug, parenteral administration is necessary. Sodium sulfapyridine may be used for this purpose, but may sclerose veins, or cause local necrosis from accidental extravasation. In the search for soluble forms of the drug, preparations of sulfapyridine in glucose solutions have been made. Blake and Haviland [1] were able to get 2 grams of sulfapyridine into solution in a liter of fluid containing equal parts of 5 per cent glucose in distilled water and physiological saline which had been brought to a boil. By using more concentrated solutions of glucose, workers in the Research Division of the Lederle Laboratories were able to dissolve greater amounts of sulfapyridine, although boiling was necessary. It was later discovered that a similar aqueous solution of sulfapyridine could be prepared with other aldohexoses or aldopentoses. Concentrations of from 5 to 30 per cent of sulfapyridine could be obtained in from 30 to 50 per cent aldehydic-sugar water solution. In this report the properties of glucose sulfapyridine will be described and clinical studies with a solution of 10 per cent sulfapyridine in 50 per cent glucose will be reported.

The clear aqueous solution of 10 per cent sulfapyridine in 50 per cent glucose varies from a light-yellow to brown in color, contains some uncombined sulfapyridine, usually in the order of from 5 to 10 per cent of the total sulfapyridine content and some uncombined glucose, but about 90 per cent of the total sulfapyridine is in the form of a complex, believed to be a Schiff's base.† On hydrolysis of this complex, by dilution, acidification or heating of the diluted complex, free sulfapyridine is obtained.

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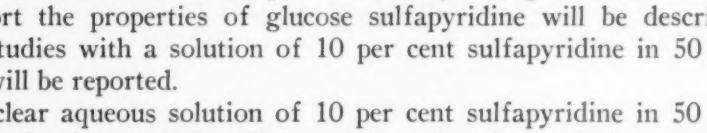
The chemical and animal studies were done at the Lederle Laboratories (Dr. Lockhart).

The clinical studies were conducted under a grant of the Josiah Macy, Jr. Foundation.

† A Schiff's base may be designated as the reaction product of an aldehyde with an amino group to form anils.



Glucose — Sulfapyridine — Glucose-anil-Sulfapyridine

Method of Assay

The method of determination of free sulfapyridine and total sulfapyridine throughout this report is that of Marshall and Bratton.[2] However, some precautions were necessary because of the tendency of the glucose sulfapyridine complex to hydrolyze rapidly on acidification. For the analysis of free sulfapyridine in glucose-sulfapyridine, the procedure must be done immediately after the bleeding or the blood sample must be kept in the chill room until analyzed. The determination in the trichloracetic acid filtrates must be done immediately after the precipitation and filtration are complete. If allowed to stand for any length of time, the acid medium is optimal for liberation of free sulfapyridine from the glucose-sulfapyridine complex. If the determinations are done at once, time and temperature will not have been able to play any rôle or to affect hydrolysis. The value obtained for free sulfapyridine, in this technic, will be the free sulfapyridine present in the blood stream when the sample was taken. The total sulfapyridine value obtained will consist of free sulfapyridine, complex sulfapyridine (glucose-anil) and acetylated sulfapyridine.

Animal Experiments

In order to determine the comparative therapeutic effect of glucose sulfapyridine and ordinary sulfapyridine, mouse protection studies were undertaken. In a series of tests involving the oral use of glucose sulfapyridine in 35 mice, and of equal amounts of a sulfapyridine suspension (with a small amount of gum acacia added to maintain a homologous mixture) in 35 other mice, no essential difference in toxicity or survival rates between the two drugs was noted. In the animals which died toxicity due to drug was differentiated from pneumonia by the presence of hematuria in the animal when alive, and the absence of pneumococci in the heart's blood when autopsied. In these experiments, the therapeutic dose of glucose sulfapyridine was so near the toxic dose that the therapeutic effect was masked. With a dose of 2 gm. per kilo per day of either drug, protection against 200 M.F.D. of virulent Type II pneumococci is approximately 70 per cent.

The relative absorption of equal amounts of sulfapyridine and of the sulfapyridine suspension given orally was studied in a group of 12 rabbits. When fed either 100 mg. or 300 mg. per kg. body weight of these drugs, the rabbits which received the glucose sulfapyridine showed the higher blood levels; this difference was more marked with the larger of the two doses used. The rapidity of absorption was about the same. These results are at variance with those obtained with patients treated with equal amounts of the two drugs. It was found that gum acacia did not influence the rate of absorption in the sulfapyridine suspension, and when absorption and protection tests were done on a group of 24 rats, results similar to those obtained with rabbits were observed.

Human Absorption of Glucose-Sulfapyridine

The absorption of glucose-sulfapyridine (10 per cent sulfapyridine in 50 per cent glucose) when administered to humans orally, intravenously, and by rectum has been studied. Frequent blood samples were taken from selected patients who received the drug by the various routes, and daily specimens were obtained from nearly all of the 130 patients with pneumonia who were treated with glucose-sulfapyridine by mouth. These oral results are to be compared with those obtained when sulfapyridine tablets are administered.

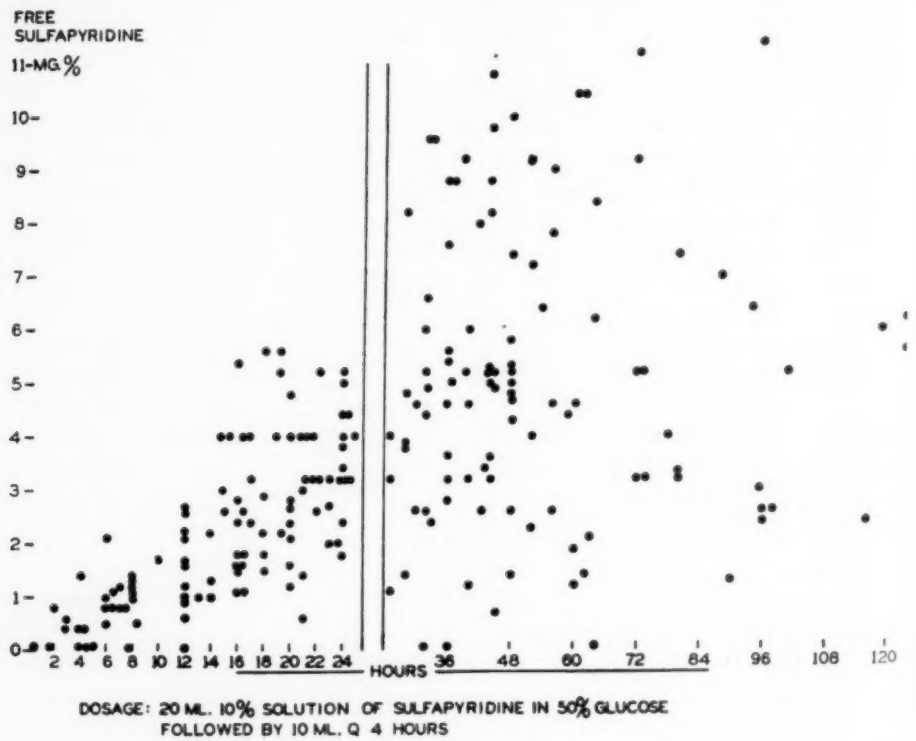


Fig. 1. Blood levels of free sulfapyridine after oral administration of glucose sulfapyridine.

Oral Administration. When glucose-sulfapyridine is given by mouth in the dosage of 2 gm. (20 c.c. of solution) followed by 1 gm. every 4 hours, the blood sulfapyridine content rises slowly but steadily for about 24 hours (figure 1). After this the absorption curve tends to level off, although as this dosage is continued, the content increases somewhat over the next 24 or 48 hours in many patients. These findings confirm those of Finland and his associates.[3, 4]

When sulfapyridine tablets are administered in the same dosage, the blood sulfapyridine content rises more rapidly, and the absorption curve tends to level off after about 12 hours; increases after this time come more slowly.

The average maximum blood sulfapyridine level obtained by the oral administration of these two compounds is about the same; the difference lies in the speed of their attainment.

In experiments concerning the anti-pneumococcal power of blood of patients receiving glucose-sulfapyridine by mouth, Finland and his associates have found that the bacteriostatic and bactericidal power of such blood is equivalent, level for level, to blood of patients receiving the ordinary sulfapyridine tablets.

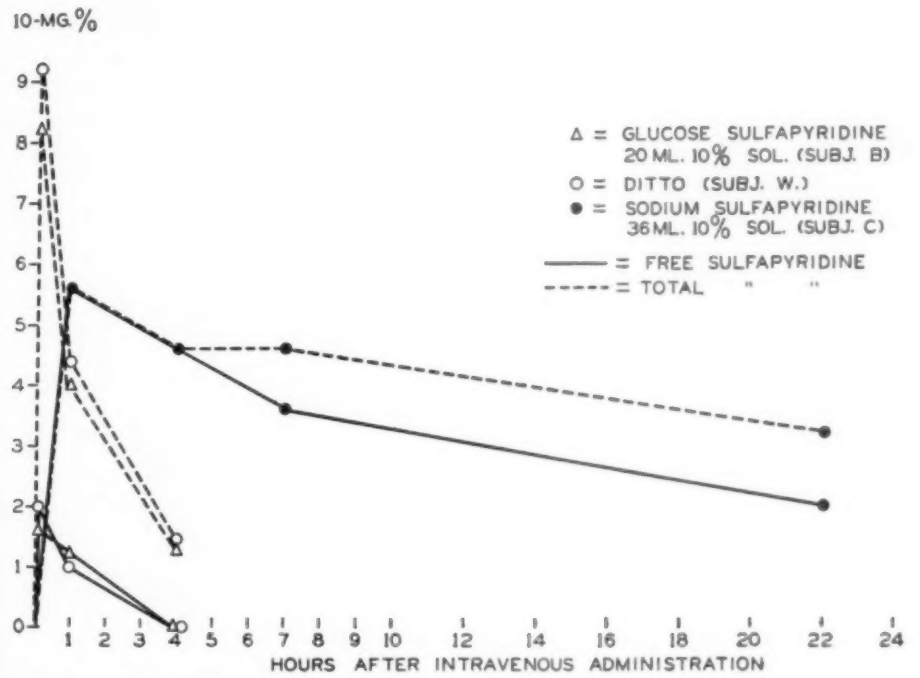


FIG. 2. Blood levels of free and total sulfapyridine after intravenous administration of glucose sulfapyridine compared with sodium sulfapyridine.

Intravenous Administration. The production of a soluble form of sulfapyridine which is not highly alkaline (as is sodium sulfapyridine, whose pH is about 11), led to the hope that the new preparation would be suitable and safe for parenteral use when indicated. Preliminary studies were first made regarding the blood levels which might be obtained after intravenous injection before using the drug by this route in pneumonia patients.

Twenty c.c. of the undiluted glucose-sulfapyridine preparation were administered slowly (2 to 3 c.c. per minute) to six selected patients on the medical wards. Patients with known kidney damage were not used, since excretion of sulfapyridine may be delayed in such patients. Frequent blood samples were taken for study.

The blood sulfapyridine content naturally rose quite rapidly (figure 2).

Three to five minutes after the completion of the injection, the total sulfapyridine content of the blood varied from 8 to 12 mg. per cent. The free sulfapyridine content at this time was low, however, varying from 1 to 2 mg. per cent. This shows that the glucose-sulfapyridine is not hydrolysed to free sulfapyridine in the blood stream. The level of both free and total sulfapyridine fell rapidly after injection, and at the end of four hours only traces of free drug and 1 to 2 mg. per cent of "total" drug remain in the blood stream. This rapid fall is due to the fact that the injected drug is excreted rapidly in the urine.

Finland and his associates[3] have reported similar findings when glucose-sulfapyridine is injected by vein in a more dilute solution. Their results differ from ours, however, in the comparative amounts of free and total drug recovered from the blood stream, the free drug apparently accounting for about 50 per cent of the total in their experiments and only 15 to 20 per cent in ours. This difference may be due to differences in method and time of assay. After intravenous administration of the glucose-sulfapyridine compound, three derivatives are found in the blood. These are (1) free sulfapyridine (since about 10 per cent of the material before administration is in the free form), (2) the glucose-anil, and (3) acetylated sulfapyridine. With the modification of Marshall's method which we use, the latter two compounds are indistinguishable under the ordinary conditions under which the estimations were carried out. The value for free sulfapyridine, on the other hand, seems to be readily estimated separately. Finland and his associates believe, however, that the free sulfapyridine and the glucose-anil test as one and the same drug under conditions prevailing in their laboratory. This probably accounts for the difference in comparative amounts of free and "total" drug which are obtained in the two laboratories. From a practical point of view our results are in agreement as to the fact that the blood level falls too rapidly after intravenous administration of glucose-sulfapyridine to make this route of injection of value. In addition, Finland's group has shown that the blood of patients who receive the glucose-sulfapyridine intravenously does not have anti-pneumococcal power.[5]

Administration by Rectum. Four patients were given cleansing enemas followed by retention enemas of glucose-sulfapyridine in 200 to 300 c.c. of tap water. Two patients were given 20 c.c. of the compound, one patient 30 c.c. and one patient 40 c.c. The tap was well retained in each case. Blood specimens were obtained 45 minutes after administration of the drug and again 24 hours later. The blood showed only traces of free drug and values of "total" drug ranging from traces to 0.8 mg. per cent; the latter figure was obtained when 40 c.c. of the compound were administered.

Clinical Results

Since October 1938 a study of the chemotherapy of pneumonia has been in progress at Bellevue Hospital. Glucose-sulfapyridine has been one of the

chemotherapeutic agents under investigation. Although it soon became evident that this preparation would not be useful for intravenous injection, it was decided to ascertain its possible value as an oral medicament. While it is possible to crush sulfapyridine tablets and suspend them in milk or water, in our experience a goodly amount of the drug was likely to remain in the bottom of the medicine glass. A soluble non-irritant preparation, such as glucose-sulfapyridine would obviate this difficulty.

During the period of investigation, 130 cases of pneumonia have been treated with glucose-sulfapyridine orally. Certain wards were set aside and all pneumonia patients entering these wards were treated with this preparation. The cases which form the material of this clinical report were, therefore, unselected. No case was included which had not either frank physical or roentgen-ray evidence of pneumonia.

On admission of each case, a blood culture was taken before treatment and subsequent cultures were done, if fever persisted. Treatment with sulfapyridine was started as soon as the clinical diagnosis had been made and blood and sputum collected for bacteriological examination. In each case the sputum was typed as soon as feasible, directly if possible, and in each case mouse typing was also done.

Thirty-two of the 130 cases received serum. The serum treated cases were not selected because of failure to respond to sulfapyridine, but because they were part of a larger alternated series of cases that,[6] on rotation by type, were due to receive serum plus sulfapyridine rather than sulfapyridine alone. Some cases due to receive serum in the alternated series did not receive it because recovery on sulfapyridine alone was obvious by the time a typing was obtained. Four cases of probable pneumococcus endocarditis (three of whom had had good initial responses to glucose-sulfapyridine) received, without effect, sodium sulfapyridine later during their course, and five other cases received initial doses of 1 to 2 gm. of sodium sulfapyridine. Sixty-five cases were under 50 years of age and 65 were 50 or over.

Results

The results in terms of mortality are shown in table 1. It will be seen that there were 127 cases of pneumococcus pneumonia and three cases of Friedländer's pneumonia. In the pneumococcus pneumonias there were 18 deaths with a gross mortality of 14 per cent. If six cases in which death occurred in less than 24 hours after admission are excluded the mortality is 9.9 per cent.

If the group of bacteremics is analyzed separately the results are 12 deaths (55 per cent) in the 22 bacteremic cases. If three 24 hour deaths are excluded, there were 9 deaths in 19 cases (47 per cent).

There were two cases of Type B Friedländer's pneumonia, one of them bacteremic. Both recovered from their pneumonia, but one who had had edema and ascites on admission died afebrile three months after admission of

TABLE I

Distribution of Cases and Mortality Rates by Types

Type	Non-Bacteremic		Bacteremic		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
			Pneumococcus Cases			
I	15	1	4	1	19	2
II	15	1	4	3	19	4
III	9	1	3	2	12	3
IV	5	0	0	0	5	0
V	9	0	1	0	10	0
VI	1	0	0	0	1	0
VII	16	2	3	2	19	4
VIII	10	0	2	0	12	0
X	3	0	0	0	3	0
XI	2	1	0	0	2	1
XII	1	0	0	0	1	0
XIII	1	0	0	0	1	0
XIV	0	0	1	1	1	1
XV	2	0	0	0	2	0
XVII	2	0	0	0	2	0
XVIII	0	0	1	1	1	1
XIX	5	0	1	1	6	1
XX	0	0	1	1	1	1
XXI	1	0	0	0	1	0
XXIV	2	0	0	0	2	0
XXV	1	0	0	0	1	0
XXIX	3	0	1	0	4	0
XXXII	2	0	0	0	2	0
Totals	105	6 (5.7%)	22	12 (55.%)	127	18 (14.%)
Excluding 24 hr. deaths	102	3 (2.9%)	19	9 (47.%)	121	12 (9.9%)
			Friedländer Cases			
A	1	1	0	0	1	1
B	1	0	1	1	2	1

cirrhosis of the liver. One case of Type A Friedländer's pneumonia (non-bacteremic) died one week after admission.

Complications. There were four cases of probable pneumococcus endocarditis with persistent bacteremia and development of cardiac murmurs (unfortunately none with autopsy); three of meningitis (one with recovery); two of grossly purulent empyema with recovery without thoracotomy on needle aspiration only; three of serous effusion who recovered with aspiration only; and two cases of otitis media.

DISCUSSION

We have noted only slight differences in the clinical effect of glucose-sulfapyridine and sulfapyridine tablets in the oral chemotherapy of pneumonia. The gross mortality rate of 14 per cent in these glucose-sulfapyridine treated pneumonias is about identical with the mortality rate (15 per cent) of a similar series of sulfapyridine treated cases reported from Bellevue

Hospital by our group. However, the results in the bacteremic cases are not as good. In the sulfapyridine series there were 35 bacteremic cases, of whom 12 died (34.3 per cent); excluding 24 hour deaths there were only 8 deaths (25.8 per cent). While the total number of bacteremic cases in each series is not large, the fact remains that the mortality rate with glucose-sulfapyridine was much higher (55 per cent for all cases, 47 per cent if 24 hour deaths are excluded). Since it is of course not possible to determine immediately which cases are bacteremic, the glucose-sulfapyridine, while apparently adequate for most non-bacteremic cases, is not to be recommended

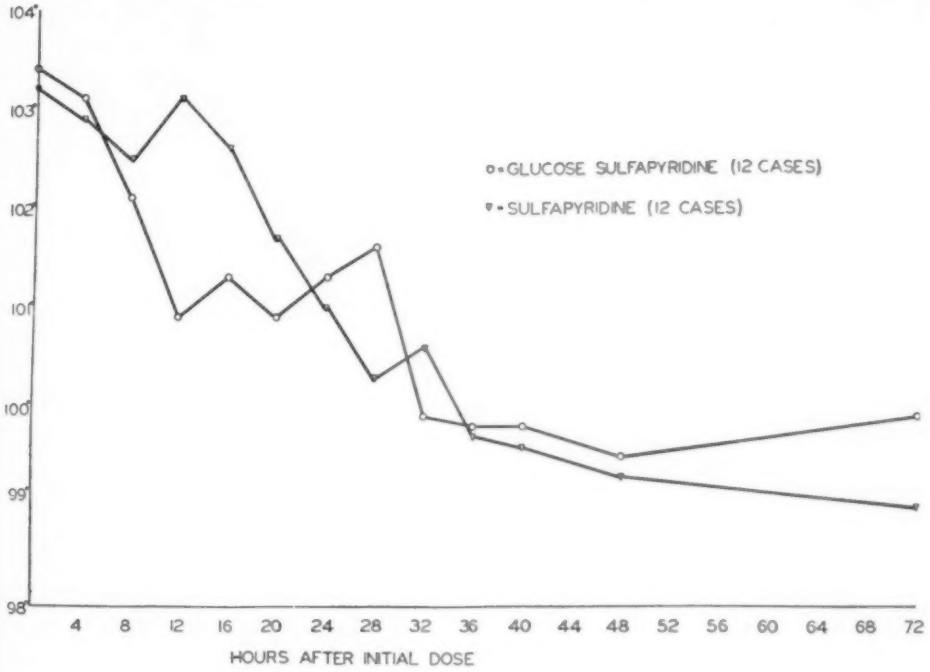


FIG. 3. Average temperature curves.

as a preparation for routine use in pneumonia. It is likely that prompt establishment of "adequate" blood levels (just what constitutes adequate levels is still not decided) is necessary in order to save the largest possible number of the seriously ill patients.

The effect on the temperature curve is essentially the same as can be seen from figure 3, which shows composite temperature curves of 12 cases (six Type I and six Type VII) treated with glucose-sulfapyridine, and 12 cases of the same types treated with sulfapyridine tablets in the same hourly dosage. These cases were the first six in each Type I and Type VII group who fell by lot into the "drug only" series for treatment by the respective agent.

There was only one case of granulocytopenia (with recovery), two mild secondary anemias, one case of gross hematuria and renal colic, and two cases of psychosis (which cleared when the drug was discontinued), and one case

of cyanosis ascribable to sulfapyridine. Nausea and vomiting seemed to be less frequent with glucose-sulfapyridine than with plain sulfapyridine tablets. Of the 130 cases 49 (38 per cent) had either nausea or nausea and vomiting. Of these 49, nine had nausea only, and of the 40 who had vomiting, this was classified as severe in seven, moderate in 24, and slight in nine cases. This figure of 38 per cent is significantly lower than the 52 per cent of nausea and vomiting in the series of sulfapyridine treated cases previously reported. We attribute this lowered incidence of nausea and vomiting to the slower rise of the absorption curve of glucose-sulfapyridine.

It is interesting to note that not only did we not infrequently see dramatic and critical falls in temperature with blood levels of less than 4 mg. per cent, but also the composite temperature curve is essentially the same as that of tablet treated cases with a more rapid rise of blood sulfapyridine.

Conclusions

1. A concentrated (10 per cent) solution of sulfapyridine has been prepared in combination with glucose, yielding what is believed to be a glucose-anil.

2. When this solution is administered orally to rats and rabbits, a higher blood level of both free and "total" sulfapyridine is obtained than with an equal amount of free sulfapyridine in suspension.

3. When 2 gm. per kilo per day of either glucose-sulfapyridine or sulfapyridine suspension are fed to mice, protection against 200 M.F.D. of virulent Type II pneumococci is approximately 70 per cent.

4. Oral administration to humans results in a delayed absorption into the blood stream, the blood curve level rising slowly for about 24 hours and then tending to level off. The relative percentage of free and total sulfapyridine in the blood stream is in the same general range obtained when ordinary sulfapyridine is given. With the latter drug absorption is more rapid.

5. Intravenous administration to humans of 20 c.c. of the glucose-sulfapyridine solution results in an immediate high level of "total" sulfapyridine but a low level (1 to 2 mg. per cent) of the free drug. Both of these levels fall very rapidly.

6. Rectal administration to humans of glucose-sulfapyridine is followed by very little absorption.

7. Only slight differences in the clinical effects of glucose-sulfapyridine and sulfapyridine tablets have been noted, and the gross mortality in the two groups is about the same. In the bacteremic cases, however, there is a distinctly higher fatality rate in the glucose-sulfapyridine group. Since it is not possible immediately to determine which patients have bacteremia, glucose-sulfapyridine is not recommended as a preparation for routine use in pneumonia.

Mr. Frank B. Ablondi performed many of the animal experiments and chemical determinations.

DEATHS

Name	Age	Type	Total Drug Gm.	Units Serum	Remarks
W. P.	54	I	145	0	Diabetes mellitus. Bacteremia on admission and persistently from 3rd week until death from pneumococcus endocarditis on 56th day. No response to either sodium sulfapyridine or sulfathiazole.
L. B.	60	I	4	0	24-hour non-bacteremic death.
P. P.	55	II	6	330 000	4 gm. glucose-sulfapyridine and 2 gm. sodium sulfapyridine I.V. Died 13½ hours after admission.
J. F.	60	II	42	170 000	Bacteremia 500 colonies per c.c. on admission. Temporary sterilization of blood stream but recurrence of bacteremia persisting in spite of sodium sulfapyridine by mouth and by vein. Died of pneumococcus endocarditis and meningitis 3 weeks after admission.
J. S.	57	II	18	0	Overwhelming bacteremia with innumerable colonies. Died 4th day.
R. W.	53	II	31	0	Bacteremia 58 and 89 colonies per c.c. Blood stream never sterilized in spite of levels of 4 to 9 mg. % (also received sodium sulfapyridine). Probable endocarditis. Died 6th hospital day.
C. V.	70	III	5	0	Admitted late in disease. Bacteremia. 18-hour death.
R. B.	64	III	32	360 000	Bacteremia 22 colonies per c.c. Arteriosclerotic heart disease with decompensation on admission. Died 6th hospital day with normal temperature.
J. B.	62	III	12	0	No response to drug in spite of good levels. At autopsy showed consolidation of RLL, LLL, and partial consolidation of RUL and LUL.
P. F.	46	VII	48	0	Bacteremia 7 and 17 colonies per c.c. Sterile at 96 hours but recurrence and persistence of bacteremia after 11th day in spite of glucose and sodium sulfapyridine. Developed aortic diastolic murmur and died one month after admission of pneumococcus endocarditis.
J. O.	52	VII	24	0	Myeloblastic leukemia with 530,000 W.B.C. and 97% myeloblasts on admission. Consolidation RUL, RLL, LLL. Died on 3rd hospital day.
W. L.	56	VII	8	400 000	Four day history of pneumonia beginning during alcoholic bout. Jaundiced on admission with consolidation of 3 lobes. Bacteremia 100 and 150 colonies per c.c. Died 45 hours after admission. Autopsy.
W. P.	55	VII	2	0	Admitted 6th day of disease, moribund, in pulmonary edema. Died 8½ hours after admission.
J. O.	66	XI	34	120 000	Admitted in diabetic acidosis which was easily controlled. Initial good response but relapsed on 5th hospital day and died on 10th day.
H. B.	65	XIV	4	0	Bacteremia 121 and 75 colonies per c.c. Died 18½ hours after admission.
W. P.	54	XVIII	26	0	Elderly hypertensive admitted on 6th day of disease with bacteremia, 150 colonies per c.c. Blood cultures persistently positive. Died with meningitis on 6th hospital day.

DEATHS—*Continued*

Name	Age	Type	Total Drug Gm.	Units Serum	Remarks
C. J.	67	XIX	2	0	Two previous admissions for arteriosclerotic heart disease with decompensation. Admitted in frank failure, with bacteremia 30 and 34 colonies per c.c. Died 16 hours.
A. A.	54	XX	18	200 000	Bacteremia with innumerable colonies on admission. Subsequent blood cultures sterile but no temperature response. Died 4th hospital day. Autopsy: Confluent lobular pneumonia entire right lung. Empyema, right. Arteriosclerotic heart disease with decompensation.
F. F.	74	Fried. A.	50		Type XXI in sputum. Friedländer Group A empyema.
J. M.	41	Fried. B.	60	0	Angiomata of face and thorax and history of pancreatitis 10 years previously. Consolidation RUL and bacteremia. Developed lung abscess one month after admission which healed by time of death, 2 months later. Jaundice present on 7th hospital day; edema and ascites on 13th hospital day. Repeated paracentesis. Afebrile death, probably from cirrhosis of the liver.

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A SYNDROME OF UPPER ESOPHAGEAL STENOSIS *

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Starvation overshadows the many other sequelae of esophageal stenosis. Pulmonary complications, for instance, unless of calamitous proportion, are often overlooked or misinterpreted. Attention is usually directed to the more dramatic accidents such as perforation into the trachea. The more frequent complications are either insufficiently emphasized or not widely appreciated. With certain types of esophageal stenosis these may occur with such constancy as to become part of the clinical syndrome.

This report concerns itself with the syndrome of aspiration of ingesta into the air passages due to esophageal stenosis. Following a review of our clinical material we felt the need for further elucidation of the symptomatology and the mechanism of the clinical picture. A plausible anatomical and physiological explanation is offered to explain the succession of events.

A brief review of the literature corroborated our impression that the origin of the pulmonary complications has received relatively little attention. McCrae [1] stated that dyspnea could be a prominent feature of carcinoma of the esophagus, even before dysphagia, if either or both of the recurrent laryngeal nerves become involved. Jackson, Tucker, and Clerf [2] found that cough may be brought on by an overflow of food and secretion from the esophagus into the larynx. Likewise, esophageal paralysis seriously interferes with swallowing. The pyriform sinuses fill and overflow into the larynx (Chevalier Jackson sign of esophageal stenosis).[3] Jackson and Jackson [4] were so impressed with the frequent oversight of the esophageal origin of pulmonary symptoms that they discussed, in a separate communication, the many ways in which this can occur. They cite aspiration of ingesta as a cause. They have had the experience that any stenosing lesion, by causing an overflow of the esophageal contents, may result in contamination of the tracheo-bronchial system. They have observed overflow with the following esophageal lesions: congenital stenosis, foreign bodies, syphilis, aneurysm, cardiospasm, and benign and malignant new growths. Recurrent laryngeal nerve involvement is also listed as a cause for aspiration. They do not mention having actually seen the overflow during a fluoroscopic examination, but have come to their conclusion from highly presumptive evidence. Vinson and Kimmelsteil [5] believe that regurgitation of mucus is inevitable in any case of complete obstruction of the esophagus. When this occurs at night, it is associated with aspiration and may lead to chronic bronchiectasis. They have noted aspiration as a complication of cardiospasm. Vinson [6] believes

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that every esophageal history should include inquiry concerning regurgitation, and whether or not this is associated with strangling as a result of aspiration into the air passages. He believes that aspiration may take place from any esophageal stenosis. However, he states [7] that "respiratory symptoms are less frequent in carcinomatous obstruction than in that from other esophageal lesions, unless the growth has penetrated the wall of the trachea or a bronchus with formation of a fistula." This last is at variance with our experience.

Mathews and Schnabel [8] investigated 108 autopsied cases of carcinoma of the esophagus. Eighty-six were of the stenosing variety; 22 of the non-stenosing type. Every lesion in the uppermost third of the esophagus was of the stenosing type. The part pneumonia played in the termination of life in the stenosing group assumed great importance, 67 per cent of this series dying from this immediate cause. The authors believe that at least some of the pneumonias were due to the aspiration of food. Keefer [9] described 17 cases of esophageal carcinoma accompanied by serious pulmonary complications. Twelve of these were caused by perforation of the cancer; only one by aspiration of ingesta into the tracheobronchial tree. He states therefore, that the majority of such pulmonary complications are usually the result of perforation into the trachea, bronchi, mediastinum, lung, or pleura. However, since he presents a highly selected group of cases, most of which perforated, we cannot conclude that in an unselected series this would be the usual mechanism of pulmonary involvement. Rastelli [10] described an interesting case of malignant stenosis at the upper end of the esophagus. His patient complained of hoarseness, cough, and dysphagia. He was emaciated, and had râles and dullness at both lung bases. The fingers were clubbed. Roentgen-ray examination of the lungs disclosed areas of increased density in the right middle and lower, and in the left lower lobes of the lung. The diagnosis was bronchopneumonia. On fluoroscopic study of the esophagus the barium was held up at the site of the lesion and then spilled over the top of the esophagus into the larynx and tracheo-bronchial tree. The right recurrent laryngeal nerve was involved causing a fixed right vocal cord. He believed that since the cords could not approximate in the midline, the ingesta had an unimpeded passage into the lung, thereby causing aspiration pneumonia.

Jousseaume [11] classifies the respiratory symptoms as laryngotracheal or pulmonary in origin. He agrees with Collet, whom he quotes, in stressing the frequent involvement of the recurrent laryngeal nerve as a factor in the production of respiratory symptoms such as hoarseness, aphonia, or stridor. He also states that bulging or fistula into the tracheo-bronchial tree may be responsible for these symptoms. However, he does not mention aspiration as a prominent cause of respiratory complaints.

In contradistinction to Jousseaume, Collet, and others who believe that the recurrent laryngeal nerve involvement is frequent with carcinoma of the esophagus, Vinson [12] in discussing his studies of 1,000 cases of esophageal

malignancy, cites only 17 instances of paralysis of one or both cords. These cases were seen in a large clinic between 1923 and 1933 and it is possible that since the involvement was not suspected, it was not sought for in each case. In a later discussion [6] the same author aptly warns that hoarseness associated with difficulty in swallowing, should suggest an esophageal lesion of malignant type.

The 30 cases which comprise this study were culled from the files of the Brooklyn Cancer Institute. However, the diagnosis of carcinoma could not be verified in each instance. Common to all was obstruction in varying degree of some part of the esophagus. Roentgen-ray and fluoroscopic examinations * of the esophagus were performed in every case. Wherever possible esophagoscopy † and roentgen-ray of the chest were also done. Cursory correlation of the pulmonary complications with the esophageal lesions led us to believe that the incidence of lung affections was greatest when the esophagus was involved in its uppermost third. The cases were then arbitrarily classified as to their location in the upper third or lower two-thirds of the esophagus. Thereafter the cases were unselected, being entered on the chart in sequence according to the patient's date of application to the clinic.

We then studied the age and sex of the patient; the type and duration of complaint; the roentgen-ray and fluoroscopic findings in the esophagus; the presence of aspiration into the tracheo-bronchial tree; the condition of the esophagus as seen by esophagoscopy; the location of the lesion; the presence or absence of vocal cord paralysis; whenever possible, the pathology of the lesion; the roentgen-ray and clinical findings in the chest; the presence of clubbing of the fingers; and finally, the course and outcome of the disease.

Analysis of the Lesions Which Involved the Uppermost Third of the Esophagus (Chart 1)

Thirteen cases, or 43.3 per cent of the total, showed involvement of the uppermost third of the esophagus. In two instances (cases 3 and 5) this involvement was secondary to lesions proximal to it. The sex incidence was as expected, there being only one female in the group. The average age was 58 plus years. The most common complaint was inability to swallow properly; but cough, hoarseness, vomiting, pain, and cervical mass were also observed. The average duration of complaints before a physician was consulted was approximately five and a half months.

Radiographic studies of the esophagus showed it to be involved primarily or secondarily in every case. Fluoroscopic examination with barium gave extremely important information. The degree of difficulty in swallowing could be visualized. More significant, the actual welling over of barium from the esophagus into the trachea could be demonstrated. This was ob-

* We wish to thank Dr. S. W. Westing, roentgenologist, for his helpful coöperation.
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CHART I

Analysis of Lesions in Upper Third of Esophagus

The Cases are Unselected, Being Entered on Chart in Succession According to Date Admitted

Case No. Date of Admission	Sex Age	Complaint	Duration in Months	Roentgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
J. D. 1 9/23/37	M 43	Vomiting Dysphagia	3	9/27/37—Swallows with greatest difficulty. Lumen of esophagus narrowed to ¼" at clavicles and dilated above this. There is long retention and delay of barium.	After several forceful acts of swallowing the barium spills over into trachea.	9/30/37—An irregular superficial mass protruded into esophagus from left anterior cricopharyngeus wall.	Uppermost portion of esophagus.	Not noted.	No evidence of malignancy.	10/4/37—No evidence of pulmonary, pleural, or mediastinal affection aside from barium in tracheo-bronchial tree.	Present.	Received roentgen therapy to the esophagus. Subsequent esophagoscopies and roentgen-ray studies reveal only scarring. Malignancy not proved. Clubbed fingers still present. Undiagnosed low grade pneumonitis due to aspiration probably accounts for clubbing.
D. D. 2 11/15/37	M 58	Mass in neck	7	11/16/37—There is a constant circular constriction at the level of the clavicles. 2/23/38—No swallowing difficulty. 3/30/38—Greatest swallowing difficulty.	3/30/38—A few drops of barium enter tracheobronchial tree by spilling over.	11/23/37—A cauliflower infiltrative lesion 18 cm. from the incisors is present on the anterior cricopharyngeus wall.	Uppermost portion of esophagus.	Both cords paralyzed in parallel position 1/25/38.	Squamous cell ca.	11/15/37—Roentgen-ray chest negative. 2/23/38—Roentgen-ray chest negative. 4/20/38—Bronchopneumonic affection of right upper two-thirds of lung (mild). Physical findings those of severe bronchopneumonia.	Absent.	Gastrostomy done but patient died 4/20/38 of aspiration bronchopneumonia.
J. G. 3 11/18/37	M 67	Mass in neck	6	11/23/37—An irregular filling defect is noted at the junction of the hypopharynx and esophagus. Swallows with greatest difficulty and pushes food down slowly.	A small quantity of barium is spilled over into the air passages.	1/11/38—There is an induration of the right aryepiglottic fold and arytenoid extending into right pyriform fossa.	Junction hypopharynx and esophagus.	Right cord paralyzed.	Epidermoid ca.	11/23/37—Obliterated costophrenic angle. 1/11/38—Some emphysema present. Developed aspiration bronchopneumonia before death.	Not noted.	Died 5/1/38 of aspiration and terminal pneumonia.

L. S. 4 1/24/38	M 47	Dysphagia	4	1/27/38—Very irregular filling defect on the posterior wall of the esophagus in its cervical portion above the clavicles. Epiglottis lacks function and there is great swallowing difficulty.	Barium spills over into the right air passages.	2/3/38—Granulation present on posterior surface of arytenoids extending into esophagus making opening of the crico-pharyngeus a hazardous procedure.	Uppermost portion of esophagus.	Right cord paralyzed.	Squamous cell ca.	1/27/38—Bronchopneumonic consolidation of right lower two-thirds apparently due to aspiration of food. Thickened bilateral apical pleura. 3/1/38—Above process more advanced. Additional lobes involved. 3/30/38—Bronchopneumonic process shows signs of clearing up (post-gastrostomy).	Present.	Patient became extremely emaciated. Bronchopneumonia due to aspiration cleared up somewhat following gastrostomy but the patient went downhill. Later tbc. isolated from sputum. Required incision and drainage of neck abscess. Died 4/19/38.
C. W. 5 4/25/38	M 60	Mass in neck	4	10/31/38—The lumen of the esophagus is narrowed to 1/8" at a point 15 cm. below incisors just below base of larynx. The narrowed area is extremely irregular in outline. There is considerable obstruction above this point.	No barium noted in tracheo-bronchial tree on single examination which was done. Later developed marked swallowing difficulty.	5/9/38—No laryngeal pathology noted. Esophagoscope passed with difficulty. There is a deformity at the upper end of the esophagus pushing the posterior wall forward. Possibly enlarged glands. 11/1/38—Friable mass found in right pyriform fossa.	Uppermost portion compressed.	No paralysis present.	Squamous cell ca.	4/25/38—No osseous or pulmonary pathology noted on chest plate. 8/22/38—Small pleural effusion right base. Thickening of the pulmonary markings, especially at the right base. 4/4/39—Coarse mottling lower two-thirds right lobe. Extensive bronchopneumonia.	Present.	The first portion of the esophagus was compressed. Only one examination done early in condition, no aspiration was noted, but he later developed great difficulty in swallowing and clinically is said to have died from aspiration bronchopneumonia 4/8/39.
J. D. 6 9/23/38	M 52	Hoarseness Dysphagia	6 2	9/26/38—20 cm. below incisors is a concentric constriction extending for 5 cm. 10/20/38—During fluoroscopic examination for localization of lesion for deep therapy department, some barium entered trachea.	9/26/38—No barium enters air passages. 10/20/38—Barium spilled over into right main bronchus.	9/29/38—Edema present in arytenoid region. Considerable mucus present. No evidence of any post-cricoid or laryngeal lesion. About 2 cm. below crico-pharyngeus, a large, granular, bleeding mass fills almost entire upper esophagus. Tracheal examination reveals lesion in lateral tracheal wall.	Upper esophagus 2 cm. below cricopharyngeus.	Paresis left cord.	Squamous cell ca. in esophagus and trachea.	9/20/38—Fibrotic changes are noted in the base of the right lung field. 10/25/38—Small areas of bronchopneumonic affection just above the right half of the diaphragm. These seen 9/20/38 called fibrotic changes are probably due to aspiration. Barium disappeared from air passages.	Absent.	Had a gastrostomy but tried to take fluid by mouth and developed aspiration bronchopneumonia. Developed cough with thick yellow brown sputum. Died 11/17/38.

CHART I (*Continued*)

Case No. Date of Admission	Sex Age	Complaint	Duration in Months	Roentgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
J. Dr. 7 9/29/38	M 61	Dysphagia Hoarseness	5 4	10/3/38—At level of clavicles, the esophagus shows a forward bulging with greatly disturbed mucosal pattern. There is no appreciable obstruction but a markedly disturbed swallowing mechanism.	10/3/38—With every act of swallowing, some barium spills over into tracheobronchial tree.	10/18/38—Lesion found on posterior esophageal wall at entrance to the esophagus. Both cords fixed leaving a chink for respiration.	Entrance to esophagus.	Both paralyzed.	Acanthosis.	10/3/38—Cherry sized area of bronchopn. 1" above rt. diaphragm. 10/24/38—Rt. lung less illuminated than left suggesting moderate atelectasis. Evidence of pn. or bronchopn. cannot be detected. 10/29/38—Both lower thirds show considerable mottling due to bronchopneumonia.	Beginning.	Patient developed a marked stridor because both cords were paralyzed. Developed an aspiration bronchopn. and died 11/1/38.
C. A. 8 10/14/38	M 63	Dysphagia Hoarseness	3 ½	10/17/38—Mucosa greatly disturbed and lumen greatly narrowed for 3.7 cm. at level of the sixth cervical vertebra. Food passage markedly delayed.	10/17/38—Not seen. Only one examination done.	10/18/38—Right cord fixed. Only slight motility of left. Marked spasm and cyanosis of patient did not allow passage of esophagoscope during evipal anesthesia.	Upper esophagus.	Right paralyzed. Left paresis.	Not obtained.	10/17/38—Rt. costophrenic angle obliterated by adhesions. 12/6/38—Trachea narrowed to less than finger width. Marked bulging into right lung field apparently due to swelling of mediastinal structures. 1/13/39—Bronchopn. both bases.	Absent.	Had tracheotomy and gastrostomy but died of bronchopneumonia 1/15/39. General anesthetic no longer given to esophagus patients before careful vocal cord examination.
F. R. 9 10/27/38	M 66	Dysphagia Hoarseness	4 1	11/3/38—At level of lower surface of the clavicles, the lumen is narrowed to 0.6 cm. for distance of 5.0 cm. Mucosal pattern destroyed with formation of a pea sized crater. From the involved area a streak of barium extends into trachea. Swallowing difficult but not delayed.	Esophago-tracheal fistula.	11/1/38—A lesion at the opening of the esophagus obstructs it 75–80%.	Uppermost portion of esophagus.	Left cord paralyzed.	Transitional cell ca.	11/2/38—Chronic inflammatory changes are noted in both bases. Right greater than left. 12/22/38—Basal one-fourth right lower lobe shows coarse mottling apparently due to bronchopneumonia. Trachea deviated to the right.	Absent.	Had gastrostomy performed but died of aspiration bronchopneumonia 12/23/38.

P. D. 10 4/22/39	M 53	Cough Dysphagia	5 4	4/24/39—Barium enters respiratory system through a perforation at the upper end of the sternum. Cause of perforation not indicated.	Esophago-tracheal fistula.	3/16/39—Esophagoscopy done elsewhere. Mass found growing from esophagus into trachea.	Upper portion of esophagus.	Right paralyzed.	Squamous cell ca. esophagus and trachea.	Clinically, had aspiration bronchopneumonia.	Absent.	Gastrostomy done, but patient died. Autopsy confirmed diagnosis—Aspiration bronchopneumonia. Died 5/4/39.
B. F. 11 6/13/39	F 57	Dysphagia	4	6/16/39—Barium stopped 2.5 cm. below sternoclavicular joint. Barium has funnel shape, the narrow end being displaced to the right and narrowed to about 1 cm. width for 10.0 cm. Patient starts coughing immediately.	Roentgen-rays taken a little later reveal a small amount of barium in tracheo-bronchial tree.	6/17/39—Cricopharyngeus is spastic and swollen. 3 cm. below the cricopharyngeus, a cauliflower growth springs from the left post. esophageal wall, partially obstructing lumen.	Upper esophagus 3 cm. below cricopharyngeus.	Right paralyzed.	Biopsy reported inflammation. Repeat requested but not obtained.	6/16/39—Small amount of barium in tracheo-bronchial tree. Intense calcification wall of aorta. No other pulmonary or pleural affection on roentgen-ray. Physical exam. shows both lung fields with coarse, moist râles.	Absent.	Sent to chronic institution where she died 7/12/39.
C. V. H. 12 6/13/39	M 54	Cough Dysphagia	12 4	6/20/39—Right pyriform sinus and 15.0 cm. of esophagus show completely disturbed mucosal pattern. Flow of barium little interfered with.	A minimal amount of barium can be noted in main right bronchus and trachea.	7/10/39—Autopsy revealed a lesion in the first 15 cm. of esophagus penetrating into trachea and almost obstructing it.	Uppermost 15 cm. of esophagus.	Left paralyzed. Right paresis.	Squamous cell ca.	6/14/39—Numerous pea and cherry sized metastases. 6/27/39—Fist sized area of pneumonic consolidation in right costophrenic angle.	Absent.	Died of aspiration bronchopneumonia 7/10/39.
P. S. 13 11/16/39	M 76	Dysphagia Pain	8	11/20/39—There is a defect in the hypopharynx and upper esophagus. Great difficulty in swallowing and spilling over of barium into respiratory system.	Barium spills over into tracheo-bronchial tree.	11/30/39—Left cord fixed. Right moves poorly. Spasm prevented further examination.	Upper esophagus near epiglottis.	Left paralyzed. Right paresis.	Not obtained.	11/24/39—Small areas of bronchopneumonia above right and left diaphragms.	Present.	Gastrostomy done. Developed popliteal artery thrombosis and aspiration bronchopneumonia. Died 12/15/39.

served during the first examination in eight of the thirteen cases. A subsequent examination in case 6 likewise demonstrated it. Thus in nine of the thirteen cases (69.2 per cent) barium was seen to spill over into the tracheo-bronchial tree. In an additional two cases (9 and 10) barium entered the air passages via fistulae (15.4 per cent). In the remaining two cases (5 and 8), aspiration could not be demonstrated during the single fluoroscopic examination which was done. However, patient 5 later developed marked swallowing difficulty and the clinical opinion as to cause of death was aspiration bronchopneumonia. Case 8 likewise, probably died of aspiration bronchopneumonia. It is felt that if follow-up examinations were done, aspiration might have been seen in every case. With some variations in each patient, the exhibition of aspiration was quite similar. There would be several forceful efforts at swallowing during which the barium would descend to the obstruction and then fill the proximal dilated portion of the esophagus. With continued swallowing efforts a variable amount of coughing would follow and then barium could be noted spilling over into the tracheo-bronchial tree. A trickle of barium could then be seen in the air passages. This could also be visualized on the radiographic films. In two of the nine cases fluoroscopy indicated severe swallowing difficulty but it was not until the films were read that barium could be detected in the tracheo-bronchial system.

Esophagoscopy showed the pathological process to be at or near the cricopharyngeus in each instance. Biopsy, when obtained, did not invariably prove the lesion malignant. Cases 3 and 5 had lesions in the pyriform sinus which interfered with esophageal function. In every patient the mechanism of swallowing was compromised.

Extremely significant was the condition of the vocal cords. Their status was noted in 12 of the 13 cases. Eleven of these 12 patients (91.6 per cent) had either one or both cords involved. No paralysis was present in patient 5 whose lesion lay in the pyriform sinus with the esophagus only secondarily affected. Patient 1 whose cords were not examined at the time of his illness, has since been examined. The cords showed good function. Malignancy was never proved in this case.

The pulmonary findings were closely associated with the phenomena of aspiration. Roentgen-ray or physical examination indicated the presence of bronchopneumonia in every case but the first (92.3 per cent). Repeated interval examinations were necessary because the pneumonic process did not become intense until late in the illness, presumably following massive or repeated aspiration. Spilling over from the esophagus into the air passages accounted for the observed pathologic process in every case but two, where esophago-tracheal fistula due to the malignancy explained it. That a low grade pneumonic process could take place due to aspiration, without roentgen-ray or physical confirmation was seemingly demonstrated in case 1. Aspiration was noted on fluoroscopy and roentgen-ray, yet no mediastinal, pleural or pulmonary pathologic process could be detected on roentgen-ray or clinical

study. However, had not his lesion been quickly relieved he probably would have gone on to develop the more advanced clinical picture. The presence of clubbed fingers in this patient, with no other apparent cause for their appearance, likewise seems to speak for a low grade, possibly long standing, pulmonary process.

The presence of clubbed fingers in more than a third of the cases (38.5 per cent) is an additional finding of interest and significance. The patients presented none of the usual causes for clubbing and we were hard pressed to explain its presence until the phenomena of aspiration were noted. We could then rationalize it on the basis of a low grade, chronic, pulmonary infection caused by repeated small aspirations. In every case which showed clubbing, except case 5, we were able to demonstrate aspiration. Only one examination was done on this patient who later developed marked swallowing difficulty. It is felt that repeated examinations would possibly have revealed it. Another patient (6) showed no aspiration during one examination, but demonstrated it during a second study. Those cases which showed aspiration, but no clubbing, possibly ran too acute a course to allow of its development.

Twelve of the 13 patients died. They all died of aspiration bronchopneumonia. Patient 1 on whom a diagnosis of malignancy was never proved, is alive. He has no swallowing difficulty at present. His chest is clear, but he still has markedly clubbed fingers. Repeated examinations have revealed no other condition which might have been responsible for their formation.

Analysis of Lesions Which Involved the Lower Two-Thirds of the Esophagus (Chart 2)

Seventeen cases, or 56.7 per cent of the total, fell into this group. Three of the patients were females. The average age was 65 plus years. The most common symptom was difficulty in swallowing, although substernal distress, expectoration, cough, and choking were noted. The patients waited an average of five months before seeking medical aid.

Roentgen-ray examination showed the esophagus to be affected in every case. Fluoroscopic observations, however, differed greatly from those found in the first group. The consistent interference with swallowing was not observed. In the two patients (17 and 18) who did have great difficulty, aspiration was demonstrated. In patient 17 barium spilled over from the esophagus into the trachea; in 18 a fistula was found. Thus in this group we could demonstrate overflow aspiration in only one case (5.9 per cent) and fistula in only one (5.9 per cent). The other 15 patients (88.2 per cent) showed no barium in the air passages. Aspiration may have been present, but was undetected in patient 27 who had bronchiectasis and later consolidation of the right lung as well as clubbed fingers; patient 29 had an abscess in the right lower lobe which likewise may have been due to aspira-

CHART II

Analysis of Lesions in Lower Two-thirds of Esophagus

The Cases Are Unselected, Being Entered on Chart in Succession According to Date Admitted

Case No. Date of Admission	Sex Age	Complaint	Duration in Months	Roentgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
J. G. 14 12/ 7/36	M 69	Dysphagia.	2	12/17/36—Between 7.5 cm. and 15 cm. above diaphragm there is concentric narrowing. No dilatation above. 2/19/37—Beginning dilatation of proximal portion.	None.	12/29/36—At about 28 cm. from the incisors is an easily dilated granulating area. 3/9/27—At about 28 cm. from the incisors is an easily dilated granulating area.	28 cm. from incisor teeth.	12/29/36 O. K. 4/9/37 Paresis right.	Squamous cell ca.	5/14/37—Roentgen-ray chest negative.	Not noted.	Gastrostomy performed. Patient died 6/24/37 of urinary retention following trauma due to falling out of bed.
L. K. 15 5/18/37	F 56	Dysphagia. Substernal distress.	3 3	5/21/37—No dilatation. No delay. Third quarter of esophagus is inhomogeneous in character.	None.	5/22/37—There is an extensive cauliflower lesion 30 cm. from the teeth.	30 cm. from incisors.	Examined but not recorded.	Acanthosis.	5/21/37—Healed calcific tbc. focus at base of left lung field with a small pleural effusion.	Not noted.	Died 10/19/37. Elsewhere.
H. F. 16 7/ 1/37	M 75	Dysphagia. Choking.	2	7/1/37—Esophagus narrowed to lead pencil width. Oral portion widened to double but fluid passes undisturbed.	None.	7/14/37—30 cm. below incisors a web constricts the esophagus. No attempt made to go beyond stricture.	30 cm. below incisors.	O. K.	Not taken.	7/1/37—Roentgen-ray of chest negative. 7/28/37—Bronchopneumonic affection of lower two-thirds of right lung and lower half of left (postoperative).	Not noted.	Patient died 7/29/37 of post-operative bronchopneumonia nine days after gastrostomy.
G. C. 17 3/ 8/38	M 59	Dysphagia.	7½	5/10/38—Swallows with difficulty. Upper half of esophagus is slightly dilated. In the center the lumen is rather abruptly narrowed to lead pencil width.	A rare drop of barium is spilled over into air passages.	Done elsewhere. Revealed carcinoma with ulceration and infection.	Middle third.	Not examined.	Squamous cell ca.	3/10/38—Two small areas of consolidation seen above left diaphragm which are probably inflammatory, but possibly neoplastic.	Not noted.	Had gastrostomy 10/18/37. Didn't show up again. Last seen 3/10/38.
R. M. 18 3/14/38	M 44	Dysphagia. Expectoration.	6 5	3/17/38—Patient swallows with difficulty. At junction of middle and lower two-thirds barium comes to a stop and from here enters left main bronchus. Further coughing interrupts study.	Esophagobronchial fistula.	Patient's condition did not warrant manipulation. Died before this could be done.	Middle third of esophagus.	Not examined.	Not taken.	3/17/38—Coarse mottling and pleural thickening in upper half right lobe and right costophrenic angle; most pronounced near hilus.	Present.	Died 3/24/38 of aspiration bronchopneumonia.

F. A. 19 5/ 3/38	M 57	Dysphagia.	6	5/5/38—A stricture is present at the arch of the aorta which narrows esophagus to lead pencil width. Hardly any delay in swallowing.	None.	4/7/38—A cauliflower growth completely obstructs lumen 12 cm. below cricopharyngeus.	12 cm. below cricopharyngeus.	O. K.	Squamous cell ca.	5/23/38—Roentgen-ray chest negative.	Absent.	Died 5/31/38 post-esophagectomy.
L. Z. 20 6/28/38	M 60	Dysphagia.	3	6/30/38—Napkin ring cauliflower new growth causing concentric partial obstruction with slight dilatation above. Moderate delay to passage of barium. Begins four fingers below clavicle. 9/9/38—Food passes without delay.	None.	7/21/38—A lobulated mass completely filled esophagus 31 cm. from incisor teeth.	31 cm. from incisors.	Examined but not recorded.	Squamous cell ca.	6/25/38—Right hilus nodes enlarged. 7/11/38—No evidence of pulmonary or cardiac pathology to explain clubbed fingers. 9/9/38—Moderate increase of pulmonary markings with right lung.	Present.	Received radiation therapy and improved. Discharged to clinic 9/20/38 and not seen since. Physical examination revealed dullness and râles both bases. Died 1/15/39 elsewhere of starvation.
A. Mc. 21 8/ 8/38	M 75	Dysphagia.	4	8/8/38—Irregularity at the lower end of the esophagus with slight dilatation and retention.	None.	8/11/38—38 cm. from the incisors the lumen is narrowed by an obstructing mass.	38 cm.	Examined but not recorded.	Squamous cell ca.	No demonstrable pathology.	Not noted.	Died 9/12/38 of hemorrhage.
H. N. 22 9/12/38	M 65	Dysphagia.	2	9/19/38—Terminal 5 cm. of the esophagus is involved with slight dilatation and retention above.	None.	9/22/38—At 40 cm. from incisors a cauliflower mass occludes lumen.	40 cm.	Examined but not recorded.	No evidence of malignancy. No repeat obtained.	No demonstrable pathology.	Not noted.	Died 9/18/38. Circulatory collapse due to inanition.
L. T. 23 9/14/38	F 58	Dysphagia.	10	9/9/38—Globular filling defects of cherry size in the distal half of esophagus.	None.	Done elsewhere. Neoplasm in esophagus just above cardiac orifice.	Lowest third.	No record. Done elsewhere.	Squamous cell ca.	9/19/38—No evidence of metastases. Decrease of pulmonary markings over both bases.	Absent.	Gastrostomy approximately June 1938. Died at home 12/8/38.
B. F. 24 9/28/38	M 70	Dysphagia.	5	9/28/38—There is a narrowing just above the diaphragm with a dilatation to twice the normal width above this.	Not seen with this examination.	Done elsewhere. Showed malignant growth lower end of esophagus.	Lower end.	No record. Done elsewhere.	Squamous cell ca.	Examination unsatisfactory.	Beginning?	Infected gastrostomy wound. Lost ground and died 11/27/38.
G. L. 25 10/15/38	M 75	Dysphagia.	1	10/17/38—Starting in the center of esophagus and extending for 4" is an irregular filling defect.	None.	10/18/38—A mass was found halfway down esophagus.	Middle third.	Examined but not recorded.	Squamous cell ca.	10/17/38—Pleural adhesions right costophrenic angle.	Not noted.	Died at home 12/27/38.

CHART II (*Continued*)

Case No. Date of Admission	Sex Age	Complaint	Duration in Months	Roentgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
M. P. 26 10/27/38	M 75	Dysphagia.	12	10/27/38—At middle third is an obstruction through which food does not pass in ½ hour.	None.	12/15/38—At approximately 27 cm. from teeth there is a proliferative, grayish growth which constricts lumen.	27 cm. from incisors.	O. K.	Squamous cell ca.	11/17/38—A spherical shadow noted just in front of new growth, apparently a mediastinal lymph node metastasis. No inflammatory pathology on roentgen-ray or physical.	Absent.	Refused gastrostomy. Died January 1939 of starvation and cerebral accident.
F. R. 27 10/31/38	M 61	Cough. Dysphagia.	9	11/29/38—Extensive lesion present in the entire lower half of esophagus with partial obstruction.	None.	Not done. Downhill course too rapid.	Entire lower half.	Not examined.	Not taken.	11/3/38—Lipiodol study indicated bronchiectasis. 12/14/38—Consolidation of the right lung.	Present.	Died 12/14/38 of bronchopneumonia. Bronchiectasis may in part account for clubbing.
E. R. 28 11/18/38	F 68	Dysphagia. Cough.	6 8	11/22/38—There is a large new growth occupying the lower half of the esophagus. Three minutes after swallowing, the esophagus is practically empty.	None.	11/29/38—Lower portion has a proliferative lesion involving the anterior wall.	Lower half.	No paralysis.	Squamous cell ca.	11/22/38—Fibrotic lesions in the subclavian region of left apex and left bronchus suggesting bronchiectases.	Absent.	Developed a severe psychosis following gastrostomy. Sank into coma and died 3/15/38.
J. Z. 29 4/20/39	M 57	Dysphagia.	2	4/25/39—There is a lesion in the esophagus extending from 4″ below the incisors to 10″ below the incisors with slight narrowing and some retention.	None.	No consent obtained.	Middle third.	Not examined.	Not obtained.	4/25/39—The right lower lobe contained a fist sized consolidation of chronic pneumonic affection with a peach sized abscess.	Not noted.	Died at another institution 5/9/39.
E. T. 30 5/ 8/39	M 64	Dysphagia.	3	5/10/39—From 5″ to 10″ from the incisors there is an absence of mucosal pattern and filling defect of the esophagus. There is slight retention and dilatation.	None.	5/12/39—There is an extensive lesion beginning below the cricopharyngeus.	Middle third.	No paralysis.	Squamous cell ca.	5/10/39—Slight clouding of the lung apex possibly tbc.	Absent.	Died at another institution 6/29/39.

tion. The complaint of dysphagia, present in all patients, undoubtedly referred to the variable amount of obstruction and delay which was noted in every instance.

Esophagoscopy was done at this institution, or elsewhere, in 14 cases. Two patients were too ill and one refused examination. The diagnosis of malignancy could not always be verified. All the lesions lay distal to the uppermost third of the esophagus.

The good function of the vocal cords in this group contrasted sharply with their dysfunction in lesions of the upper third. However, some difficulty was encountered in the tabulation of results of these cord examinations. This arose because when the cords functioned well, a record of their status was not always entered on the patient's chart. Whenever done, but not recorded, this was indicated in the individual tabulations. In only one instance (14) was any affection noted, and in this patient only a weakness was seen.

Pulmonary complications were greatly reduced in this group. Ten patients had either no demonstrable pulmonary lesions (14, 19, 21 22) or lesions probably unrelated to the esophagus (15, 16, 23, 25, 28, and 30). The two patients with aspiration (17, 18) showed pulmonary pathologic findings related to it. The first had two small areas of consolidation, probably inflammatory, and the second, as expected, died of bronchopneumonia due to massive aspiration. Patients 20 and 26 showed glands in the mediastinum. These were in the region of the site of the lesion in the esophagus and were either metastatic, inflammatory or both. In any case, their presence could safely be attributed to the esophageal malignant growth. Patient 27 had a severe cough and lipiodol study indicated the presence of bronchiectasis. Patient 29 had a peach-sized abscess in the right lower lobe. Unfortunately, he refused further examinations and the mechanism of its formation could not be probed further. The lesions in both of these cases may have been due to undetected aspiration.

Clubbed fingers were present in three cases (18, 20, 27). The esophagobronchial fistula explained its occurrence in patient 18. Patient 20 showed enlargement of the hilar nodes and increased markings of the right lung field. A mediastinitis, inflammatory or neoplastic, may well have been present to account for the clubbing. Patient 27 was shown by lipiodol study to have bronchiectasis. This is an accepted cause for clubbing which possibly had no relationship to the esophageal lesion, or it may have been due to undetected aspiration.

All of the patients died. Whereas aspiration bronchopneumonia was the cause of death in every instance in the first group, among these patients the cause varied. One patient (14) died of trauma and urinary retention following a fall. Two died postoperatively; one (16) from bronchopneumonia; another (19) following esophagectomy. Patients 20 and 22 died of starvation and inanition. Starvation undoubtedly played some part in all these cases. Patient 21 died from hemorrhage; another (23) from a

severely infected gastrostomy wound. Patient 26 suffered from a cerebral accident and 28 from a severe psychosis. Both went quickly downhill and died. Five patients (15, 22, 25, 29, 30) died elsewhere without accurate diagnoses and one patient (17) could not be traced. Patient 18 who had a fistula died of aspiration bronchopneumonia.

Discussion

The symptoms and complications of esophageal neoplasms are best classified according to the location of the process. A syndrome which deserves further emphasis appears when the uppermost third of the esophagus is involved.

Features common to all of these lesions are:

a. Location at or near the uppermost portion of the esophagus.
b. Paralysis or paresis of one or both vocal cords.
c. Dysphagia.
d. Aspiration of ingesta into the tracheo-bronchial tree.
e. Pulmonary complications due to aspiration.
f. Frequent occurrence of clubbed fingers.

The normal act of swallowing is a delicately coördinated combination of acts. After mastication the food is rolled into a bolus and propelled to the back of the mouth. By a series of automatic movements the posterior nares and mouth cavity are shut off. The larynx is pulled upward under cover of the root of the tongue and the vocal cords approximated to close off the air passages. At the same time the epiglottis forms a floor over which the bolus travels to the back of the pharynx and downward by peristalsis through the esophagus.

An obstructive and infiltrative lesion at the uppermost portion of the esophagus, which involves one or both recurrent laryngeal nerves, not only disrupts the normal act of swallowing at a vital point, but opens the passage to the tracheo-bronchial tree by fixing some of the structures and interfering with the approximation of the vocal cords. Under such circumstances, aspiration would not only be likely but well nigh unavoidable.

In general this appears to be the mechanism at work in the cases located in the uppermost third. The lesion disrupts the peristalsis at the very opening of the esophagus, at the same time that the obstruction causes a damming back of the ingested material. In addition, some of the important structures, such as the epiglottis, may be fixed by the lesion. Simultaneously, the smooth coördination of the laryngeal elements is broken by involvement of the recurrent laryngeal nerve or nerves. The action of the inferior pharyngeal constrictors is somewhat distorted, but more important, the vocal cords fail to approximate and close off the air passages. The ingesta spills over the dammed esophagus into the larynx and aspiration is inevitable. Pulmonary complications, varying with the amount and type of aspiration, are

certain. Twelve patients with lesions in the upper esophagus all died of aspiration bronchopneumonia. Prior to the development of this terminal complication, varying inflammatory processes were observed. The presence of clubbed fingers in more than a third of these patients is similarly predicated on the aspiration.

The incidence of pulmonary complications dropped perceptibly when the esophageal lesions lay distal to its uppermost third. Aspiration as a cause, was proved in only one case. It might have been undetected in some others. Vocal cord function remained intact, as compared to almost universal dysfunction in the first group.

This can readily be understood when one considers the anatomical relationship of the recurrent laryngeal nerves to the esophagus. In the uppermost third both nerves lie proximal to it. On the right, the nerve loses contact with the esophagus below the subclavian artery. On the left it remains close to it down to the arch of the aorta. The dysfunction of the vocal cords associated with lesions in the uppermost portion of the esophagus is therefore easily explained. In lesions of the distal two-thirds, no cord dysfunction is noted because the recurrent laryngeals are no longer in proximity to the esophagus. The findings are therefore consistent with the anatomical facts.

With lesions in the distal two-thirds of the esophagus, the low incidence of pulmonary complications appears related to the infrequency with which early overflow aspiration is encountered. The intact vocal cord function constitutes an additional protection. The vocal cord status is not known in the one patient of the second group who had aspiration. It is possible that the carcinoma infiltrated upward sufficiently to involve one of the nerves. It is likely, however, that although a combination of factors, as seen in the first group, makes aspiration almost inescapable—all these factors are not essential. It appears reasonable to expect it when the back damming is great, and the general condition of the patient is poor, even when the lesion is in the distal two-thirds of the esophagus. This has been observed by other workers with stenosis of the distal end due to cardiospasm. Although all protective reflexes may remain anatomically intact—a general state of inanition might so raise the threshold of response and result in such sluggishness of reflex activity as to cause gross dysfunction.

The esophageal lesions in this study were mainly neoplastic. It would appear, however, that neoplasia is not an absolute prerequisite for this syndrome. Nor need the recurrent laryngeal nerves be involved. Aspiration, with its attendant complications, might be expected with any obstructive and disruptive lesion at the upper end of the esophagus, or about its opening as with lesions in the hypopharynx or pyriform sinuses. Lesions in the larynx must certainly give varying amounts of aspiration. Neoplastic stenosis in the upper esophagus, however, makes for such a combination of anatomical and physiological pathology as to make aspiration almost inevitable.

Clinically, the lungs appear tolerant to the dripping of foreign material. Large or repeated aspirations, however, must eventually produce manifest signs and symptoms. As a corollary to this, the finding of pulmonary pathologic conditions, vocal cord paralysis, or clubbed fingers in the absence of a known primary should point strongly to the esophagus or its neighboring structures as the offender. The picture of strangulation following attempts at swallowing, heretofore considered pathognomonic of esophagotracheal or bronchial fistula, must be revised to include the described possibility. Fluoroscopic barium study of the swallowing function, in addition to the esophageal study itself, should be routine in the examination of all esophageal lesions. It would be wise to incorporate this examination in the study of any lesion which might interfere with swallowing.

Summary and Conclusions

1. The findings in 30 consecutive patients who presented themselves at the Brooklyn Cancer Institute with esophageal complaints are analyzed.

2. The symptoms and complications of esophageal neoplasms are best classified according to the location of the process.

3. A syndrome which deserves further emphasis appears when the uppermost portion of the esophagus is involved. The common features of these lesions are:

a. Location at or near the uppermost portion of the esophagus.
b. Paralysis or paresis of one or both vocal cords.
c. Dysphagia.
d. Aspiration of ingesta into the tracheo-bronchial tree.
e. Pulmonary complications resulting from aspiration.
f. Frequent occurrence of clubbed fingers.

Aspiration pneumonia was responsible for all the deaths in this group.

4. The incidence of pulmonary complications dropped sharply when the esophageal pathology lay in its lowermost two-thirds. Likewise, the recurrent laryngeal nerve involvement, almost universal in the first group, was absent here. Even in this group, however, there was sufficient dysfunction to cause a rare instance of aspiration.

5. Although the esophageal lesions in this study were mainly neoplastic, it would appear that neoplasia is not an absolute prerequisite for this syndrome. Any combination of factors which resulted in similar anatomic or physiologic dysfunction might be expected to lead to similar complications.

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THE DEVELOPMENT OF PLASMA PREPARATIONS FOR TRANSFUSIONS *

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Experimentally plasma or serum was used as far back as 1871 by Bowditch [1] and a year later by Luciani.[2] A very extensive bibliography of the earlier experimental works on serum and plasma is contained in Amberson's review.[3] In 1918 Ward,[4] a captain in the British army, made a terse appeal for the use of citrated plasma in the treatment of emergencies at the clearing stations, and briefly outlined the advantages over whole blood.

As far as we know his appeal was not answered, and probably the first extensive clinical use of serum and plasma was begun by one of us in 1927. By 1931 citrated blood plasma was used routinely at the Bryn Mawr Hospital, in place of whole blood, especially in the treatment of certain hemorrhagic diseases and of streptococcic and pneumococcic diseases with publication of one of the outstanding cases by Nicholson.[5] At that time plasma was used fresh, that is blood was collected, the cellular elements were separated by centrifugation, the plasma removed by suction, mixed with an equal part of saline or saline glucose solution, to dilute isoagglutinins, and administered within 24 hours. This method of preparation of plasma remains the ideal method for securing, with relatively simple technic and elementary aseptic precautions, a safe material containing all the properties of blood plasma. It is, however, not practical, because it deprives plasma of one of its essential advantages, namely that of being immediately available for use in emergencies.

The widespread, practical use of plasma, particularly in emergencies, is dependent upon a proper method of preservation. It is this phase that we want to discuss in this brief review. Full consideration of this important problem is justified by the ever increasing number of clinical indications for the use of plasma.

A proper method of preservation may be considered one which, in the simplest manner, assures a safe sterile plasma possessing as many of the original properties as possible, and therefore having the largest therapeutic field of application.

The first method of preservation was naturally the keeping of plasma in the refrigerator at a temperature of + 6 to + 8° C. in the liquid state. We noted very soon that this method, while very simple, was accompanied by progressive flocculation of the most unstable proteins, with consequent necessity for filtration. Among the early workers using citrated plasma for transfusion must be remembered Palazzo and Tenconi [6] and Kartašhevskiy

* Read at the Boston meeting of the American College of Physicians, April 24, 1941.

and Filatov.[7] The latter stated that the fibrin-like filaments forming in liquid plasma on standing would disappear on heating, a phenomenon which we have been unable to confirm. Kartašhevskiy and Filatov used refrigerated plasma up to 11 months old particularly for the treatment of hemorrhagic diseases.

At least one death has been reported due to the transfusion of citrated plasma preserved in the refrigerator in the liquid state, without previous filtration. This case, attended by Dr. J. H. Lewis, was brought to our attention by Dr. Cooksey of Detroit. The patient, a boy, had not previously received any other transfusion. The plasma was given for the correction of hypoproteinemia and extensive edema in the course of a nephritis. The patient received 90 to 100 c.c. of undiluted plasma, in 20 to 25 minutes. Asphyxial death was sudden and occurred while the plasma was still being administered. This plasma had been separated from citrated blood about 24 hours after collection of the blood, and it had been preserved in the liquid state for 40 to 50 hours. The plasma was not filtered, and evidence points to the presence of precipitates in it before administration. Microscopic examination of the lungs (figure 1) showed extensive embolism of the smaller branches of the pulmonary artery by a pinkish staining material, with a coarse reticular structure, closely resembling fibrin. Sections from other organs showed no such changes, since the fibrin-like precipitates had not gone through the filter of the lungs.

Another danger associated with the preservation of plasma in the liquid state is bacterial contamination. A chance contamination of the blood at the time of collection or during the process of preparation affords the organisms a favorable medium of growth so long as blood or plasma is kept in the liquid state. Addition of bacteriostatic substances is of relative value only, and should not be relied upon too much. Merthiolate, which has been most commonly used, has no appreciable effect in whole blood. The addition of sulphonamids proposed by Novak [8] and others opens a more hopeful field.

Administration of plasma in which even a minimal bacterial growth has occurred causes severe reactions. Recently after the safe administration of over two thousand transfusions of plasma, mostly preserved in the liquid state, we had the experience of five such severe reactions, all from the same lot of contaminated plasma.[9] Although bacteria could not be obtained in culture, probably due to the action of the merthiolate, they could be demonstrated in the smears from sediment obtained by prolonged centrifugation of the plasma in question. Danger of such chance contaminations may be reduced to a minimum only by the adoption of strictly aseptic precautions in the collection of the blood and by the employment of a closed system for the separation, pooling and distribution of the plasma.[10] Excessive growth of a chance contaminant of plasma, with production of toxic pyrogenic substances, is best prevented by adoption of a method of preservation of plasma other than in the liquid state, as will be pointed out later.

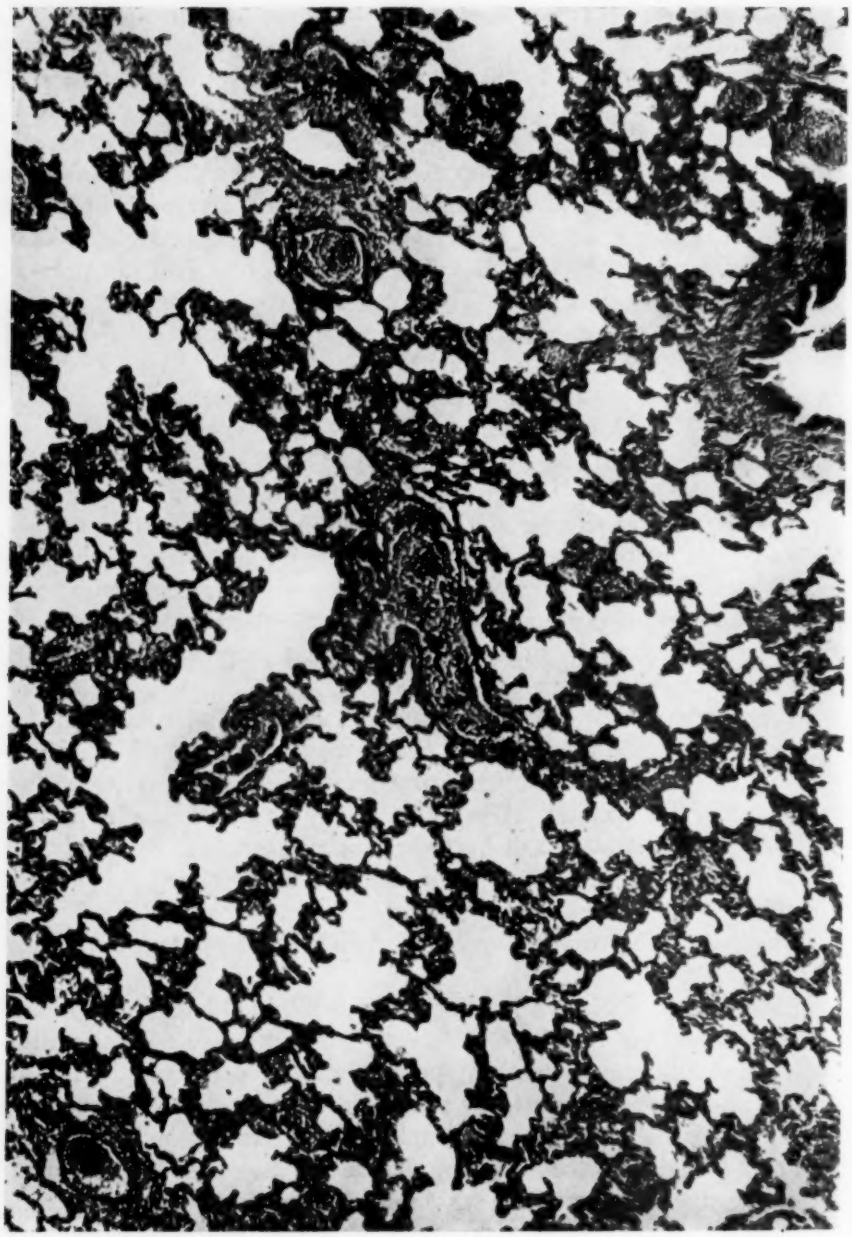

FIG. 1 *a*. Multiple emboli of fibrin-like substance in branches of the pulmonary artery. × 64.

A third objection to the storage of plasma in the liquid state is that there is a continuous and progressive loss of essential elements with aging, particularly of prothrombin and complement. This accompanies the flocculation already mentioned. Among the early advocates of the use of blood plasma is Elliot.[11] He and his co-workers[12] have recently recom-

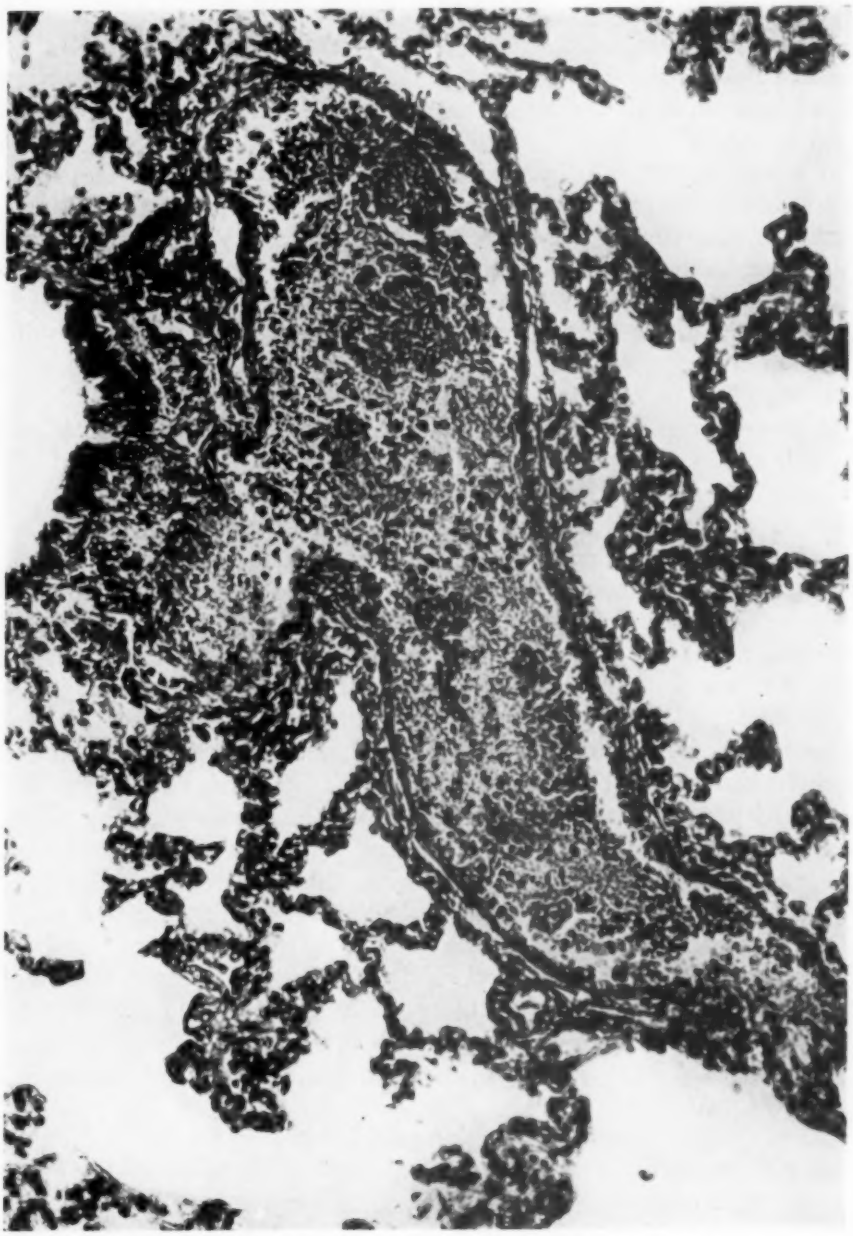

FIG. 1 *b*. Higher power magnification of embolus in a branch of the pulmonary artery. × 236.

mended dilution of plasma with glucose solution to improve the preservation. The benefits from this procedure, however, are limited. For the reasons given above it is apparent that preservation of plasma in the liquid state at 4° C. is to be discouraged.

The essential principles of drying of biological substances for the purpose of preservation laid down in the early part of the century by Vansteenberghe,[13] Bordas and d'Arsonval,[14] Shackell,[15] Harris [16] and Rogers [17] were applied later on to the developments of methods suitable for the drying of serum by Elser,[18] Reichel,[19] Flosdorf and Mudd.[20] Clinical applications of dried serum were made by Aldrich [21] and Jeans [22] for the treatment of nephrosis, by Hughes [23] for the relief of intracranial pressure, by Ravdin [24] for the treatment of hypoproteinemias, by Bond and Wright [25] for shock in experimental animals. Dried plasma was used by Mahoney [26] for treatment of experimental shock in laboratory animals, and Thompson [27] used the same material to prevent hypo-proteinemias and wound disruption in experimental animals.

Successful use of dried plasma in humans was begun in 1938 at the Bryn Mawr Hospital. The material was used especially for the treatment of shock and hypoproteinemias.[28]

Since that time observations on the safety and efficacy of dried plasma or serum prepared by various methods have rapidly accumulated and numerous other methods of drying have been proposed, too numerous to mention. It would be entirely out of place to enter into the discussion of the relative merits or demerits of these methods. It will be sufficient to state that an acceptable method of drying of plasma must yield a product which is sterile, contains as many of the original properties of plasma as possible, is readily soluble, and has less than 1 per cent of residual moisture.

Recently in connection with work done under the auspices of the National Research Council, several hundred lots of plasma, each containing 17½ to 18 gm. of plasma proteins were dried from the frozen state by a method employing the water vapor condensation by low temperature in vacuo. This material was distributed for experimental study to various institutions throughout the country, in receptacles allowing for regeneration with distilled water and direct administration. No reactions were reported in any of these tests except an occasional mild urticaria. The advantages of dried plasma are essentially the possibility of long storage and transportation under adverse conditions of climate, with opportunity for rapid restoration in emergencies. Furthermore dried plasma allows for restoration in concentrated form.

The drying of plasma, although a very interesting process and important under certain conditions, must not be allowed to overshadow the essentials of the general question of preservation as well as the practical consideration of clinical applications. The disadvantages of dried plasma are primarily the technical difficulties of its preparation, and consequently the high cost of the material, as well as the inability to maintain any appreciable amount of prothrombin in the material thus prepared. It also appears that in the ordinary conditions of hospital procedure it is rather useless to remove water from plasma only to add it a few days later when a better method of preservation is available.

As far back as 1932 during an outbreak of poliomyelitis, it was found by one of us [28b] that plasma in the frozen state could be maintained for long periods of time without appreciable loss of any of its essential properties. However, on thawing flocculation occurred, which necessitated filtration before administration. Plasma thus prepared was used intravenously without reactions on numerous occasions. Thawing was done slowly, either at room temperature or at 4° C. in the refrigerator. More recently, having reached the conclusion that drying of plasma could not for the reasons just mentioned solve the problem of preservation satisfactorily under all conditions, studies were resumed on the effect of temperature on the stability of plasma proteins. It was thus found that fresh plasma, just separated from citrated blood, will remain clear for relatively long periods of time, if kept at room temperature in the neighborhood of 25° C., but will rapidly flocculate if placed at 4° C. It was also found that if frozen plasma is thawed rapidly in the water bath at 37° C. and allowed to warm to room temperature before being removed from the water bath, it could be kept at room temperature without visible flocculation for a relatively long period of time. However, if the plasma was removed from the water bath before it had a chance to warm at room temperature flocculation occurred, whether subsequently placed at 4° C. or kept at room temperature. The initial freezing temperature and the temperature of preservation do not appear to be critical, so long as they are well below freezing in the order of —10 to —20° C. However, the time of thawing is critical, and it should be accomplished in 20 to 30 minutes at 37° C. for optimal results.

Plasma frozen, maintained for several months in the frozen state and rapidly thawed in the manner described is practically indistinguishable from the original fresh material in the matter of turbidity (figure 2), content of all essential elements including the labile ones such as prothrombin, and therapeutic action. Plasma thus obtained has been successfully used at the Bryn Mawr Hospital routinely for several months. There have been no reactions.

It must be emphasized that regardless of the adequacy of the method of preservation, the final product can be no better than the plasma as originally separated from the blood. This emphasizes the necessity not only of the already mentioned aseptic precautions and the use of a closed method, but the shortening as much as possible of the time interval between collection of citrated blood and fixation of plasma by freezing. In this connection, separation of plasma by centrifugation must be mentioned as an essential step in the securing of an optimal product.

The advantages of preservation of plasma in the frozen state are: the simplicity and economy of the method making it available to any hospital; the ease of storage and transportation; the optimal preservation of the more labile elements such as prothrombin and complement; the elimination of flocculation; and finally, the maintenance of sterility.

The employment of freezing and maintenance in the frozen state as a routine method of preservation of human plasma is not difficult because of the large variety of low temperature freezing cabinets now on the market for preservation of foodstuffs. Transportation of the frozen material for use away from the point of production or storage may be accomplished with the aid of CO_2 ice or in large quantities in refrigerated trucks. However,

FIG. 2. Effects of various means of preservation of citrated plasma.

1	2	3	4
Preserved in the liquid state at 25° C. for 21 days. Note moderate turbidity, but absence of visible precipitates.	Dried from the frozen state, regenerated with distilled water after 20 days and kept 24 hours at room temperature. Note considerable turbidity.	Frozen and kept in the frozen state for 20 days. Thawed rapidly at 37° C. and kept 24 hours at 25° C. Note maximal clarity.	Preserved in the liquid state at 4° C. for 21 days. Note flocculent precipitate.

All specimens are from the same lot of pooled citrated plasma (R.C. 57 A.)

most cases requiring transportation will be practically handled by properly melting and warming of the frozen material at the place of storage. After this, it may be sent away for use to almost any distant point and will remain free of precipitate for several days so long as it is maintained at approximately 25° C. However, it is not advisable to keep plasma in the liquid state any longer than is necessary for the reasons outlined earlier. Thawed out plasma may be refrozen, if not used, without appreciable damage to its essential elements.

Thus plasma preserved in the frozen state possesses none of the disadvantages which led to the abandonment of storage in the liquid state, namely, ease of contamination, flocculation, and progressive loss of essential elements.

In comparing dried and frozen plasma, the latter is seen to be superior in all but two respects. The dried material may be transported with greater ease under adverse conditions and it may be restored to a concentrated form if such be desired. It is estimated, that, in ordinary hospital routine and in emergency work, under the usual circumstances, over 90 per cent of the total need for plasma may be best met with material preserved in the frozen state.

Every hospital may be easily provided with means of preserving plasma by freezing. Larger and better equipped hospitals may coöperate with many smaller institutions and easily dry plasma on a scale large enough to provide for the need of all. In this manner, with judicious use of frozen and dried material, the needs of everyone will be adequately met.

The preservation of plasma in the frozen state opens the possibility for large scale storage of plasma for possible use in local or national emergencies. The material stored in standard containers may, when needed, be distributed either in the frozen state, or in the liquid state, after proper thawing, for immediate use; finally, it may be dried from the frozen state, to meet needs as they arise.

This method of combining preservation of the bulk of plasma in the frozen state, with possibility of drying at any time, does away with the expensive practice of drying of large stores of plasma.

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TOXIC DEPRESSION OF THE MYELOID ELEMENTS FOLLOWING THERAPY WITH THE SULFONAMIDES; REPORT OF 8 CASES *

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The discovery of the therapeutic effectiveness of sulfanilamide and its related substances constitutes one of the greatest advances in medical therapeutics rivaling that of arsphenamine and its compounds in the treatment of lues, and that of quinine in the treatment of malaria.

The medical profession embraced these new drugs with great enthusiasm, and their use became widespread. Soon, however, reports of toxicity following the administration of these related substances appeared in the literature. Leukopenia, granulocytopenia and agranulocytosis were three of the more serious of the toxic manifestations.

Young [1] in 1937, and Johnston [2] in 1938 were the first to report cases of agranulocytosis following the administration of sulfanilamide and sulfapyridine respectively. Since then, there have been other reports of the occurrence of this complication. Filler,[22] and Kennedy and Finland [23] in January 1941 reported the occurrence of agranulocytosis following the use of sulfamethylthiazole and sulfathiazole respectively. In this communication, we wish to record cases of leukopenia and agranulocytosis which have occurred in The Bronx Hospital following the use of neoprontosil, sulfanilamide and sulfapyridine.

Case Reports

Case 1. Leukopenia following sulfanilamide therapy. I. R., a nine-year-old girl, was admitted to the Surgical Service of Dr. J. Cohen of the Bronx Hospital on February 7, 1939 for a painful swelling of the right forearm of one day's duration. Physical examination revealed an acutely ill child with a temperature of 104.2° F., pulse of 128, and respirations 28 per minute. On the lateral proximal portion of the right forearm there was an irregular, tender, erythematous, indurated area, two by three inches in diameter. There were lymphangitic streaks extending up the medial and lateral aspects of the arm. The right epitrochlear and axillary lymph nodes were enlarged. There were no other abnormal findings. A diagnosis of erysipelas, lymphangitis and lymphadenitis was made and wet dressings ordered applied locally. The next morning it was found that the lesion had spread, the temperature had risen to 104.6° F., and the pulse rate had increased to 132 per minute. Sulfanilamide was started at 9:30 a.m., 20 gr. (1.3 gm.) being given at once and 10 gr. (0.6 gm.) ordered every six hours. The infection responded well to this therapy, and in 24 hours the temperature dropped to normal and the erythematous area began to fade and diminish in size. However, after the patient had received 65 gr. (4.3 gm.) of sulfanilamide (last dose at 10 a.m. on February 9), it was discovered that she was developing a leuko-

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From The Bronx Hospital, New York.

penia, and the drug was discontinued at once. In spite of its discontinuance, the number of white cells continued to decrease, and by the morning of February 11 was 3800 per cu. mm. (table 1). The patient was given pentnucleotide 10 c.c. twice a day and 5 c.c. liver extract twice a day. She also received 1200 c.c. of citrated blood on February 11 and 12 in divided doses of 200 c.c. each. Following these measures she improved rapidly and was discharged on February 15.

Comment: A leukopenia, which was recognized early, developed after 65 gr. (4.3 gm.) of sulfanilamide. The number of white blood cells continued to fall for two days after the drug was discontinued. A good response followed energetic therapy.

TABLE I

	Hemoglobin % Sahli	Red Blood Cells	White Blood Cells	Band Forms	Polymorphonuclears	Lymphocytes	Monocytes
Feb. 8	96	5,320,000	14,950	10	54	30	6
					Sulfanilamide given		
Feb. 9	90		6,500	10	48	42	
Feb. 10, 9 a.m.			5,200	6	44	46	
Feb. 10, 6 p.m.			4,600	18	30	52	
Feb. 11, 11 a.m.			3,800	3	27	64	4
Feb. 11, 10 p.m.			14,000	28	40	32	
Feb. 12	116	6,210,000	20,550	22	64	14	
Feb. 13			20,200	18	76	6	
Feb. 14	96	4,860,000	11,600	6	68	26	

Case 2. Agranulocytosis following sulfanilamide therapy. I. C., a 62-year-old white male, was admitted on December 23, 1938 to the Genito-Urinary Service of Dr. M. Loeb complaining of nocturia, frequency and dribbling of four years' duration. Cystoscopy revealed trabeculation of the bladder and an enlarged prostate. The patient left the hospital against advice on December 29, 1938. He stayed at home for an interval of about six weeks, during which time he became weak, lost his appetite, lost weight, and developed a swelling of his left testicle. He passed blood clots and calculi in his urine on February 8, 1939, and was readmitted to the hospital on February 10, 1939, with a temperature of 100.9° F., and pulse of 100 per minute. Physical examination revealed an elderly male subacutely ill. The skin showed evidence of loss of weight. The tonsils were hypertrophied and cryptic, the gums were infected and the submaxillary glands were enlarged. There were moist râles at both bases and in the left axilla. The heart had a regular sinus rhythm; there was a systolic blow over the apex and aortic area. Blood pressure was 126 mm. mercury systolic and 68 mm. diastolic. Abdomen was negative. Rectal examination revealed a moderately hard, markedly hypertrophied prostate. The left epididymis was swollen and tender. Laboratory data: Urine-specific gravity ranged between 1.012 and 1.018; albumin between one and two plus; sugar negative; microscopic, numerous white blood cells and red cells. Blood: Hemoglobin 82 per cent Sahli, red blood cells 5,020,000, white blood cells 7200; polymorphonuclears 71 per cent, lymphocytes 15 per cent, monocytes 3 per cent, eosinophiles 1 per cent. Wassermann and Kahn tests negative. Blood chemistry normal. Examination of the passed calculus showed it to consist of calcium oxalate and fibrin.

Electrocardiogram was negative on two occasions.

Cystoscopies on February 15 and February 23 revealed a marked hypertrophy of the prostate and trabeculation of the bladder. The bladder contained much blood and

encrusted pus. On March 4 a suprapubic cystotomy was performed. The next day the patient had an attack of pain in the right chest, accompanied by hemoptysis, cyanosis, and dyspnea. His temperature rose to 104° F., and the pulse to 120 per minute. A diagnosis of pulmonary infarction was made, and the patient was placed in an oxygen tent where he was kept for four days. On March 11 it was found that the suprapubic wound was infected, the culture showing gram positive cocci overgrown by *Bacillus proteus*. On March 14 the patient developed sticking pain in the left chest. The next day bronchial breathing was heard over the left lower lobe. A roentgen-ray of the lungs revealed irregular infiltration of both bases, interpreted as bronchopneumonia.

To combat the bladder infection, sulfanilamide was started on March 13, 1 gm. every four hours. This was given until March 19. On March 24 sulfanilamide was resumed, 10 gr. being given twice daily until April 8. The patient's temperature, which fluctuated between 100–103° F. between March 13 and March 25, gradually subsided to 99.4° F. by April 1. On April 6 the patient was given a blood transfusion of 500 c.c. On April 7 his temperature rose suddenly to 103° F. A blood count taken on April 8 revealed a hemoglobin of 52 per cent Sahli, red blood cells 2,800,000, white blood cells 2150, with a differential of 3 per cent band forms, 82 per cent polymorphonuclears and 15 per cent lymphocytes. The sulfanilamide was discontinued at once. On this day the sulfanilamide blood level was 2.2 mg. per cent. The next day, April 9, the patient's temperature rose to 104° F.; he vomited and had liquid stools. Examination of the blood at this time revealed a white cell count of 3250, but no polymorphonuclears were found. Examination of the bone marrow (sternal puncture) revealed an aplastic type of agranulocytic marrow. (See table 2 for detailed description.)

TABLE II

Case 2

	Hemoglobin % Sahli	Red Blood Cells	White Blood Cells	Band Forms %	Polymorphonuclears	Eosinophiles	Lymphocytes	Monocytes	Plasma cells
Feb. 12	82	5,020,000	7,200		71	1	25	3	
Mar. 18	54	3,500,000	13,000	8	70		18	4	
Apr. 8	52	2,800,000	2,150	3	82		15		
Apr. 9	50		3,250	Only lymphocytes on smear.					
Apr. 10	82	4,080,000	700				99		1
Apr. 11	82	3,980,000	450				99		1

Apr. 11, bleeding time 2½ minutes—coagulation time 2½ minutes.

On April 9 the nose and throat consultant found a beefy red tongue and dry mucous membranes. The tip of the tongue showed slight edema. The surface of the left tonsil had a slight grayish discoloration, apparently the beginning of a necrotic patch. The nasal mucosa was dry and slightly yellowish. His impression was agranulocytic angina in the pre-ulcerative stage.

The patient was given liver extract, pentnucleotide and two blood transfusions. But in spite of the fact that his hemoglobin rose to 82 per cent and red blood cells to 4,080,000, the white blood cells dropped to 450 per cu. mm. with no granulocytes. His temperature rose to 105.6° F.; his respiration became rapid and very shallow; and he expired on April 11.

Necropsy findings were as follows (Courtesy of Dr. Joseph Felsen):

Gross Pathology: Multiple ulcers of skin about cystotomy wound.

Hemorrhagic cystitis	Prostatic hypertrophy
Diverticulosis coli	Induration of the pancreas
Congestion of liver and spleen	Membranous gastritis

Congestion of lower lobes of both lungs with multiple infarction.
Small atheromata of aorta and pulmonary artery.

Histopathology:

Lungs: There was marked congestion of the pulmonary vessels with partial atelectasis and pulmonary edema. Another section showed vascular thrombosis with infarction of the adjacent pulmonary tissue.

Liver: There was congestion of the liver sinusoids (chronic passive congestion). The sinusoids were markedly dilated in one section. There was an encapsulated area of focal calcific deposit present.

Kidney: There was marked degenerative disease of both the parenchymatous and glomerular elements. The former showed marked cloudy swelling and glandular degeneration with separation of cells from the basement membrane. The latter were the seat of chronic fibrotic change. There were many areas of focal necrosis with round cell infiltration. A few focal areas of calcific changes were seen. A subcapsular papillary adenoma was present.

Bladder: There was necrosis of the mucosa with diffuse round cell infiltration. There were focal areas of similar nature deeper in the wall, but no polymorphonuclear cells were seen. There was considerable edema of the serosa, and numerous multinucleated giant cells were present.

Prostate: Showed considerable fibrous change. Many of the glands were cystic and lined by atrophic epithelium. A large degeneration cyst was present.

Pancreas: A fine diffuse fibrosis was present, with numerous focal areas of fat deposit.

Stomach: Section taken through membranous area showed most intense necrosis of tissue with interspersed foci of clumped bacteria.

Vertebral bone marrow: The marrow was quite fatty and showed an apparent deficiency in granulocyte production. Many megakaryocytes were present.

Smears from the spleen and liver disclosed large numbers of gram positive spore-bearing bacilli.

Sternal bone marrow examination on April 10 revealed the following: Leukocytes —2150 per cu. mm. Nucleated red blood cells 900 per cu. mm. No megakaryocytes were seen. Leukocyte—red blood cell ratio equals 2.3:1. Differential: promyelocytes 0.5 per cent, myeloblasts 3.5 per cent, lymphocytes 55 per cent, monocytes 2 per cent, reticular cells 1 per cent, Turck cells 3.5 per cent, plasma cells 4 per cent, erythroblasts 8 per cent, normoblasts 20 per cent, megaloblasts 2.5 per cent.

Interpretation: marked depression of all elements of bone marrow. Granulocytes are absent except for their earlier precursors, the marrow consisting chiefly of a few nucleated red cells and mononuclear cells of various types: the hypoplastic or aplastic type of agranulocytic marrow.

Comment: A case of agranulocytosis following the administration of 45 gm. sulfanilamide which ended fatally in spite of therapy. As in the previous case the white count continued to fall in spite of the discontinuance of the drug.

Case 3. Agranulocytosis following sulfanilamide therapy. M. N., a 39-year-old white male, was admitted to the private service of Dr. Paul Gutman of the Bronx Hospital with a history of chills, fever, myalgia and sore throat of three to four days'

duration. He was given salicylates by his physician on the first day and then received 4 gm. sulfanilamide on the third day. After he received the sulfanilamide he began to vomit profusely, and his general condition became worse. He became delirious and was referred to the hospital on July 14, 1939 at 3:30 p.m. There was no history of the ingestion of drugs prior to this illness, except that he took aspirin for headaches. Upon admission physical examination revealed a delirious middle-aged white male with a temperature of 105.2° F., pulse rate of 110, blood pressure 120 mm. Hg systolic and 85 mm. diastolic, and respiration of 22.

The pharynx was markedly congested, and there were exudates over both tonsils and posterior pillars. The cervical glands were enlarged. Heart, lungs and abdomen were negative. About two hours after admission a punctiform erythematous rash appeared over the patient's body, particularly over the lower anterior chest and abdomen.

Laboratory Data: Urine specific gravity 1.018, albumin 2 plus, sugar and acetone negative. Microscopic examination revealed many cellular and granular casts. Blood sulfanilamide 4.7 mg. per 100 c.c. Blood culture negative. Blood: Hemoglobin, 94 per cent (13.6 gm.), red blood cells 4,700,000, and white blood cells 600. Differential: No polymorphonuclears, lymphocytes 90 per cent, monocytes 10 per cent.

A diagnosis of agranulocytosis was made and the patient was immediately given a transfusion of 500 c.c. of citrated blood and liver extract parenterally.

The next morning a blood examination revealed 900 white blood cells with 94 per cent lymphocytes and 6 per cent monocytes. Another blood transfusion of 350 c.c. was given, but the patient's condition remained the same and he expired suddenly that evening.

Postmortem examination (necropsy was performed by Dr. Louis Lefkowitz, Assistant Medical Examiner of Bronx County, about 17 hours after death):

There was diffuse erythema of the skin over the lower part of the chest anteriorly. There were no petechiae.

Gross: The brain was normal. There was no intracranial hemorrhage.

Chest: The pleural cavities were clear. The lungs were deeply congested particularly so posteriorly on both sides. No consolidation was evident. The bronchi and pulmonary vessels were normal.

Heart: The pericardium was normal and contained a normal amount of clear serous fluid. The left ventricle was moderately hypertrophied. The musculature was pale. A few yellowish plaques were present on the mitral cusps; otherwise the valves were normal. The coronary arteries were normal. The aorta showed a few atheromatous plaques in the abdominal portion.

Abdomen: The peritoneal cavity was clear.

Stomach: The mucosa was intensely hemorrhagic throughout; there were discrete hemorrhagic flecks and spots scattered on all walls. The intestines were normal.

Liver: The liver was normal except for the presence of deep congestion on section.

Kidneys: Both kidneys were larger than normal. The capsules stripped readily but left large depressed stellate scars which were apparently old. On section, the cortex was somewhat reduced and the markings were distinct. The pelves, ureters, and bladder were normal. The prostate was normal. The pancreas and adrenals normal.

Spleen: The spleen was four times the normal size. The malpighian bodies were not seen.

Testicles: The right was missing. The left was normal.

Sternum: The sternum on section showed a dark red marrow. Microscopically a section of the sternum revealed a well functioning bone marrow with active production of megakaryocytes, erythrocytes, and myelocytes in various stages of maturation. Unfortunately, permission for microscopic study of the other organs was not granted by the medical examiner.

Comment: The marked vomiting, the rash, and the absence of any other predisposing drug all point to sulfanilamide as the cause of the agranulocytosis.

Case 4. The next two cases of agranulocytosis, while not unequivocal, may be due to a combination of sulfanilamide and prontosil therapy.

A. E., a 66-year-old white woman, developed a sore throat and fever on August 15, 1939. The next day a diagnosis of diphtheria was made by Dr. I. Greenberg, a physician of South Fallsburg, New York, and 5000 units of diphtheria antitoxin were administered. The diagnosis was confirmed by the New York State Department of Health Laboratories. The patient did not improve, and her temperature rose to 104° F. on August 18. Neoprontosil (20 c.c.) was given intramuscularly; sulfanilamide (gr. 5 every three hours) was started and eight doses were given. However, she did not improve, and developed definite ulcerations of the throat and palate by August 20. A smear taken from the ulcerations revealed Vincent's organisms. Gentian violet was then applied locally and 0.6 gm. neosalvarsan was given intravenously. The lesions in her mouth improved, but her general condition became worse. Her temperature rose to 105° F., and the respirations increased to 48 per minute. She was admitted to The Bronx Hospital on August 24, to the private medical service of Dr. S. Stein.

Physical examination upon admission revealed a very acutely ill, elderly female, somewhat cyanotic. The tongue was dry and crusted. The mucous membranes of the mouth were tinted with gentian violet. There was slight ulceration of the posterior palate. The heart was negative except for a sinus tachycardia. Examination of the lungs revealed impaired resonance and râles at both bases.

Laboratory data: Examination of the blood revealed a hemoglobin of 90 per cent Sahli, red blood cells 4,300,000, and white blood cells 1200. The differential revealed 2 per cent polymorphonuclears, 82 per cent lymphocytes, 2 per cent monocytes, 14 per cent plasma cells, and 2 per cent normoblasts. All the polymorphonuclears had toxic granules. Roentgen-ray of the chest was negative. Throat culture was negative for diphtheria.

The patient sank rapidly and expired a few hours after admission to the hospital.

Comment: Very thorough questioning of the family, Dr. I. Greenberg, and Dr. S. Stein, her family physician, failed to elicit the history of the ingestion of drugs for two years prior to this illness. A single dose of arsphenamine has been reported to have produced agranulocytosis,[3] although the usual occurrence is an aplasia of all bone marrow elements, which did not take place in this instance. Sepsis, per se, may also cause depression of the myeloid elements. However, in view of the rather frequent occurrences of agranulocytosis following the use of sulfonamides as compared to the rare occurrence due to neoarsphenamine and sepsis, we feel that the sulfanilamide and the neoprontosil (totaling about 50 gr.) were at least partly instrumental in having caused the agranulocytosis.

Case 5. Agranulocytosis and toxic hepatitis following sulfanilamide. F. A. was admitted to The Bronx Hospital on February 25, 1939, to the private medical service of Dr. J. Fink. She gave the following history. Five weeks prior to admission she developed acute follicular tonsillitis. She was attended by Dr. J. Fink who gave her 12 capsules, each containing five grains of antipyrine salicylate and ¼ grain of codeine. After taking eight capsules in a period of three days she improved. About February 15 she felt "grippy." She did not call her physician but took the remaining four capsules. She felt better after that and remained well until February 23, when she had

chills, sore throat, diffuse pains and aches, and temperature of 105° F. Examination at that time revealed a small exudate on the right tonsil. A culture for diphtheria was negative. A smear showed numerous cocci in chains. On February 24 she was given 1 gm. of sulfanilamide at 1 p.m. and again at 5 p.m. At 9 p.m. she received 10 c.c. of 5 per cent neoprontosil intravenously. That night her temperature rose to 106.4° F.; she was nauseated and vomited. The next morning she received 1 gm. of sulfanilamide. However, because her general condition became worse she was sent to the hospital.

Physical examination on admission revealed an acutely ill and restless young female, with a temperature of 105.8° F., pulse of 120, and respiration of 26 per minute. The mucous membranes were cyanotic. The throat revealed grayish exudates over both tonsils that could easily be removed by swabbing. The cervical glands were enlarged. The rest of the examination was negative. A blood examination on February 25 revealed the following: Hemoglobin 77 per cent, red blood cells 4,300,000, white blood cells 370, with a differential of 3 per cent polymorphonuclears and 97 per cent lymphocytes. The patient was given a transfusion of 300 c.c. citrated blood. On February 26 the exudate of the throat was more pronounced, and there was an ulceration of the left tonsil. The sternal bone marrow examined on February 27 was typical of the hypoplastic type of agranulocytic marrow, showing chiefly lymphocytes together with a few plasma and reticular cells. The granulocytes were markedly decreased in numbers. These few had toxic granules. On the same day the patient received 500 c.c. of citrated blood, and was started on Ironyl (Pentnucleotide plus liver extract). On February 28 it was observed that the patient was jaundiced, but her throat and general condition were definitely improved. From February 28 to March 4 the patient received four additional blood transfusions. She continued to improve slowly, and the number of white blood cells rose day by day, so that they numbered 8000 on March 13, a day prior to her discharge from the hospital (for blood studies see table 3).

TABLE III

Case 5

	Hemoglobin % Sahli	Red Blood Cells	White Blood Cells	Band Forms %	Polymorphonuclears	Lymphocytes	Monocytes	Transfusion
Feb. 25	77	4,300,000	370		3	97		300 c.c.
Feb. 27			830	40	10	46	3	500 c.c.
Feb. 28			1,050	31	15	51	3	300 c.c.
April 1			1,700	14	23	52	10	300 c.c.
2	76	4,500,000	1,650	6	16	74	3	300 c.c.
3			1,350	11	13	66	6	300 c.c.
4			2,300	8	10	74	8	
6			3,600	8	30	60	2	
7			4,900	11	38	50	1	
8			5,100	6	44	47	3	
9			6,350	8	55	32	5	
11			5,300	7	48	37	8	
13			8,000	2	67	29	2	

February 27, Sternal puncture: Leukocytes—5700 per cu. mm. Nucleated red cells—800 per cu. mm. Megakaryocytes—none seen. Nucleated white blood cells: red blood cell ratio was 7:1. Differential: polymorphonuclears 2 per cent, band forms 8 per cent, young forms 1 per cent, myeloblasts 1 per cent, lymphocytes 71 per cent, monocytes 1 per cent, reticular cells 1 per cent, plasma cells 2 per cent, normoblasts 5 per cent, erythroblasts 6 per cent, megaloblasts 1 per cent.

Comment: The patient took 40 grains of antipyrine salicylate five weeks prior to admission and 20 grains about 10 days prior to admission. She received a total of 3.5 gm. sulfanilamide and neoprontosil. Whether antipyrine can produce agranulocytosis is still a debatable point. If it does, it must be a very rare occurrence, as there are only two cases on record (Groen and Gelderman [4]) of this complication.

Case 6. Leukopenia due to a combination of sulfapyridine plus neoprontosil therapy. F. A., a 41-year-old white female, was admitted to the private surgical service of Dr. H. J. Epstein on July 5, 1939, because of frequency and incontinence of urine of one and one-half years' duration. Five years previously she had been treated for a kidney infection. Physical examination was normal except for the presence of a cystorectocele. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The laboratory findings were as follows: Urine—specific gravity 1.018, albumin trace; microscopic—numerous white blood cells, occasionally in clumps. Blood: hemoglobin 78 per cent (11.3 gm.), red blood cells 4,400,000, white blood cells 9,800 with 74 per cent polymorphonuclear leukocytes, 3 per cent band forms, 15 per cent lymphocytes, 5 per cent monocytes, 2 per cent basophiles, and 1 per cent eosinophiles.

On July 6, under spinal anesthesia, the patient had a repair of the cystorectocele. The temperature was normal until the second postoperative day when it rose to 104° F. associated with a chill. She was thought to have pneumonia and was started on sulfapyridine. The temperature fell the next day to 100.4° F., and the sulfapyridine was stopped. (A roentgenogram of the chest on July 10 was normal except for an elevated right diaphragm.) However, the temperature started to rise again and on the fifth postoperative day, July 11, reached 105° F. and 106° F. The temperature was associated with frequent chills, frequency and incontinence of urine. The urine, at this time, revealed one plus albumin, numerous white blood cells with occasional clumps and one or two red blood cells per high power field. *Bacillus coli* was found on culture. A diagnosis of pyelitis was made and the sulfapyridine was resumed. Thereafter the temperature was septic in type, varying from 99–106° F., with frequent chills. Repeated blood cultures were sterile. On July 13 the blood sulfapyridine concentration was 5.9 mg. per cent. After having received 20 gm. in a period of seven days, the sulfapyridine was discontinued on July 15 because it was ineffectual. Neoprontosil was started on July 20 but was discontinued on July 22 for the same reason, after a total of 6 grams had been given.

The patient developed a moderate anemia and a leukocytosis and polynucleosis which, on July 13, the seventh postoperative day, reached 14,500 with 78 polymorphonuclear leukocytes and 11 band forms. From this day forward the total number of leukocytes gradually fell. By July 26, the twentieth postoperative day, they numbered 2,050 with a differential of 56 per cent polymorphonuclear leukocytes, 27 per cent band forms, 11 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophiles. On this day the blood and urine sulfanilamide concentrations were zero. The white cells rose to 2,900 on July 29, the day she expired. She received 300 c.c. of whole blood on July 21 and 500 c.c. daily from July 23 until her death on July 29. In addition, from July 26 on, she was given leukocytic (bone marrow) and liver extracts. (See table 4 for blood studies.)

On July 15, the blood chemistry revealed non-protein nitrogen 146.4 mg. per cent, urea nitrogen 85.7 mg. per cent, uric acid 7.2 mg. per cent and creatinine 4.16 mg. per cent. She was treated by continuous infusions of 5–10 per cent glucose in normal saline, and by July 23 the non-protein nitrogen had fallen to 50 mg. per cent. Cystoscopy and excretion urography showed right kidney pathology. On July 23 her right kidney was decapsulated and a cortical abscess of the upper pole was excised by Dr.

TABLE IV

Case 6

	Hemoglobin % Sahli	Red Blood Cells	White Blood Cells	Polymorphonuclears	Band Forms	Lymphocytes	Monocytes	Eosinophiles	Basophiles	Plasma	Sulfapyridine concentration
July 5 Admission	78	4,400,000	9,800	74	3	15	5	1	2		
July 8	84		24,350	96		4					
July 11	68	3,650,000	13,400	76	10	14					
July 12	62		13,900	70	18	4	6	1		1	
July 13	70		14,500	78	11	9	2				5.9 mg.
July 14	70		12,000	72	16	5	7				
July 17	76	3,900,000	11,800	76	9	12	3				
July 19	68	3,700,000	9,200	53	26	16	5				
July 21	62		9,200								
July 22	58		7,600	50	20	24	4	1	1		
July 24	54	3,000,000	4,900	44	27	23	4			2	
July 25	70	3,700,000	3,300	58	22	16	4				
July 25			3,100	28	28	36	8				
July 26	74	3,800,000	2,900	40	22	28	10				.0 mg.
July 26			2,050	56	27	11	5	1			
July 27			2,500	26	32	21	8	2	1		
July 28	88	4,600,000	2,900	42	43	10	2	2	1		

Martin Loeb. A culture from the abscess was sterile after 72 hours' incubation. Histologically, a section of the renal cortex showed acute and chronic pyelonephritis. Following the operation the nitrogenous elements of the blood fell to normal. Nonprotein nitrogen 25 mg. per cent, uric acid 3.1 mg. per cent, creatinine 1.4 mg. per cent. The patient's condition, however, became steadily worse, and she expired at 6:05 a.m. July 29, 1939. (See table 5 for blood chemistry studies.)

TABLE V

Case 6

	Blood Chemistry: Glucose	Non-Protein Nitrogen	Urea N	Uric Acid	Creatinine	CO_2 Combining Power
July 15		115.4				52.2
	97.1	146.4	85.7	7.2	4.16	
July 16		105.3				
July 17	95.3	67.4	37.5	4.6	1.49	
July 18	104.7	47.6	25.6	5.2	1.17	
July 20		48.4				
July 23		50.2				
		50				
July 24	173.9	41.4	12.7	4.1	1.39	
July 25	87	25.9	12.9	3.1	1.40	

The urinalyses throughout the course showed a specific gravity varying from 1.005 to 1.013, 2–3 plus albumin, a moderate to a marked number of white blood cells with a moderate to a marked clumping tendency, and from an occasional to many red blood cells. Cultures revealed *Bacillus coli* and *Staphylococcus albus.*

Necropsy (Courtesy of Dr. Joseph Felsen):

Gross findings: Pulmonary edema and congestion. Red hepatization of the left lower lobe. Chronic passive congestion of the liver. Multiple cortical thromboses of

the left kidney with several small abscesses. Right pyohydronephrosis with gangrenous pyelitis, ureteritis and cystitis. Multiple hemorrhagic ulcerations of the ascending colon.

Microscopic findings: There were focal areas of necrosis in the lungs, spleen, liver, pancreas and kidney which contained giant cells in their centers. These lesions were strongly suggestive of tuberculosis. The bone marrow section revealed some areas of focal necrosis, but other areas revealed active cell production and maturation and many megakaryocytes.

Comment: The total number of white blood cells began to fall a day before the sulfapyridine was discontinued, i.e., after a total of 19 grams had been given, and then reached a level for a few days. Following the discontinuance of the neoprontosil therapy, they decreased a little more rapidly and were at their lowest level four days after the latter drug was stopped. The total dosage of both drugs was 26 grams over a period of 14 days, with a lapse of five days following the discontinuance of the sulfapyridine before the neoprontosil was given. Repeated transfusions, liver and bone marrow extracts brought about a slight increase in the number of white blood cells. However, the patient died before any real effect of this therapy could be noted, though histologically the bone marrow showed active cell production and maturation.

Case 7. Agranulocytosis following sulfapyridine therapy. M. K., a 45-year-old white male painter, was admitted to the medical service of Dr. Henry Schumer on January 4, 1940 because of fever 99–102° F. daily, anorexia, loss of weight and profuse sweats for six weeks. He had been in the hospital from October 23, 1939 to November 18, 1939 for a chronic sacroiliac strain. During that time he ran a low grade temperature, the cause of which was not determined. Blood culture was negative. His past history revealed the knowledge of the presence of a heart murmur for 22 years. There was no rheumatic history.

Physical examination revealed a chronically ill, well-developed, well-nourished male showing evidence of recent weight loss. The skin was warm and moist. The temperature was 101° F., the pulse 120, and respirations 24 per minute. The mucous membranes were pale. The fundi were normal. The lungs were essentially negative. The heart was not enlarged. The sounds were of good quality and A_2 was greater than P_2. There was a systolic thrill at the apex, and a rough blowing systolic murmur was heard over the entire precordium, loudest at the apex where it occupied all of systole. Blood pressure was 138 mm. Hg systolic and 64 mm. diastolic. There was tenderness in the epigastrium and the right upper quadrant, with resistance in the latter area. The edge of the liver was palpated two fingers below the costal margin. The spleen was not felt. Right costovertebral tenderness was present. There was a left scrotal hernia. There was bilateral unsustained ankle clonus, more marked on the right side. No Babinski sign was present. No petechiae were found.

Laboratory examinations: The urine was normal. Blood: Hemoglobin 68 per cent (9.9 gm.), red blood cells 3,500,000, white blood cells 17,200, polymorphonuclears 83 per cent, band forms 1 per cent, lymphocytes 10 per cent, monocytes 6 per cent. The sedimentation rate was 40 mm. (Wintrobe). There were no tubercle bacilli in the sputum. The blood chemical tests were normal.

The admission diagnosis was subacute bacterial endocarditis.

Course: On January 9, 1940 the blood culture which was taken on admission was reported to contain 240 colonies of *Streptococcus viridans*, alpha type, per cubic centimeter of blood. The patient was then started on sulfapyridine, one gram every

four hours. The temperature, which had ranged from 101 to 103° F., immediately fell to 99° F. within 24 hours and continued about 100° F. until January 15. Then it began to fluctuate between 100–103° F. until January 20 when it again fell to 100–101° F. It continued at this level until January 25 when the sulfapyridine was discontinued because of the development of agranulocytosis. It rose terminally to 104° F. The total dose given was 89 grams. The blood sulfapyridine level during therapy ranged between 2.9 mg. per cent and 8.9 mg. per cent. The sulfapyridine was continued in spite of a poor response to its use as a preliminary to heparin therapy which was not instituted because of the development of an agranulocytic state.

During the first week the pulse was about 100; thereafter it ranged about 120 per minute, and gallop rhythm was present at the apex. The respirations were normal the first week, 20–22, slightly increased the second, 22–28, and moderately so thereafter, 24–36.

The patient went steadily downhill. Blood cultures remained positive. Blood studies showed a secondary anemia of moderate degree and a leukocytosis with polynucleosis. Moist râles were heard at the bases of the lungs from January 5 on. A roentgenogram of the chest on January 9 showed increased markings at the bases, more marked on the right side, and a slightly enlarged left ventricle. On January 23 sacral and ankle edema were first noted, and the liver, which had been about two fingers'-breadth below the costal margin, was now four fingers'-breadth below. The spleen was still not palpable. On this day, too, fundal hemorrhages and red blood cells in the urine were found for the first time as evidence of embolization. At 5 p.m. on January 23 the patient had a sudden attack of severe painless dyspnea and cyanosis. At this time the respirations were 36 per minute, the pulse 136 and the blood pressure 136 mm. Hg systolic and 66 mm. diastolic. There were diminished breath sounds and moist râles over the bases of both lungs. He was thought to have a pulmonary infarction. He was placed in an oxygen tent and was digitalized because of his congestive failure. An electrocardiogram on January 24 showed findings suggestive of a coronary occlusion. The icteric index on January 25 was elevated to 12.5. Another electrocardiogram on January 26 suggested the presence of a previous coronary occlusion and myocardial fibrosis. The patient who up to and including January 23 had a leukocytosis and a polynucleosis was found on January 25 to have a granulocytopenia with a leukocyte count of 776, polymorphonuclears 11 per cent, lymphocytes 69 per cent, monocytes 21 per cent. The sulfapyridine therapy was stopped. At this time the blood sulfapyridine level was 5 mg. per cent. The sternal marrow findings revealed an almost complete absence of the granulocytic elements. That afternoon a citrate transfusion of 500 c.c. of blood was given and pentnucleotide 10 c.c. intramuscularly four times a day was started. By the afternoon of January 26 the white count had risen to 1344 but the polymorphonuclear leukocytes had fallen to 2 per cent with a rise in the lymphocytes to 98 per cent. Thrombopenia and abnormal clotting time were associated. No mouth lesions were present. The dyspnea continued; the edema increased; and the abdomen became distended. The patient did not respond to prostigmin. He expired at 3 a.m. on January 27, 1940, 23 days after admission. A sternal marrow examination performed 15 minutes after death was essentially similar to the previous one except that no granulocytic elements were present. (See table 6 for blood studies.)

Postmortem examination: (Necropsy was performed seven hours after death by Drs. Kastl and Rothstein):

There was edema of the dependent parts and slight scleral jaundice. Petechiae were present in the right lower lid and over the chest and abdomen. No lesions of the mucous membranes of the mouth or pharynx were present.

Lungs: A moderate amount of pulmonary edema and congestion of the bases was present. Microscopic examination showed a large amount of pulmonary congestion.

TABLE VI

Case 7, M. K.

Date	Red Blood Cells Millions	Hemoglobin Per Cent Sahli	White Blood Cells	Nucleated Red Blood Cells	Neutrophiles	Band Forms	Lymphocytes	Monocytes	Eosinophiles	Nucleated Erythrocytes	Basophiles	Platelets	Clot Retraction	Bleeding Time	Coagulation Time	Red Cell Fragility	Icteric Index	Blood Sulfanilamide mg. %	Blood Culture Colonies per c.c.	Hippuric Acid Synthesis	Congo Red %
1/4	3,500,000	68 (9.99) gm.	17,200		83	1	10	6											240		
1/8																				3.36 g. excreted	50%
1/10		61 (8.9) gm.	11,900																		
1/11		66 (9.69) gm.	22,400															5.0	260		
1/12	3,600,000	66 (9.69) gm.	16,000		91	3	5	1													
1/13																		3.3			
1/15	3,500,000	68 (9.9) gm.																			
1/16		62 (9)	10,100															2.9			
1/17																			300		
1/18		56 (8.1) gm.	13,200															7.1			
1/20																		8.0			
1/22																		8.9			
1/23		57	13,100											1½	3				500		
1/25, 10 a.m.	3,800,000	68 (9.9) gm.	776	144	5		79	0	16	16							12.5				
11:30 a.m.			776	194	11		67	21		19		30,000									
3 p.m.	4,100,000	66 (9.16) gm.	2,116	184	14		72	0	14	8		50,000							Transfusion 500 c.c. 4:30 p.m.		
1/26, 10 a.m.	3,800,000	68 (9.9) gm.	1,020	180	1		71		28	15		70,000	none after 24 hours			0.38 to 0.30	14.1		Smear of red blood cells, anisocytosis, poikilocytosis, macrocytes, microcytes, polychromatophiles.		
2:30 p.m.			1,344	306	2		98			18		40,000		1½	4½						

The alveoli were the seat of exudative and cellular changes. The intra-alveolar cells were largely mononuclear. Some atelectasis was present.

Heart: The heart was enlarged, weighing 700 grams. The pericardial sac contained 15 c.c. of serous fluid. Both ventricles were hypertrophied, the left being dilated. Examination of the valves showed numerous grayish-red vegetations on the mitral, aortic and the tricuspid valves. The mitral valve exhibited extensive ulceration of the leaflets. Several vegetations were seen on the left auricular endocardium, smears of which showed gram positive cocci in chains. The papillary muscles and chordae tendineae appeared hypertrophied. The coronary arteries showed slight atherosclerosis especially at their origin. On microscopic examination, the valves showed fibrinoid changes with necrosis and bacterial clumping. The underlying tissue of the valve was extremely cellular and contained many small and large mononuclear cells. Occasional giant cells and some fibroblasts were present. Considerable hyaline, myxomatous and fibrinoid degeneration was present. The endocardium exhibited similar changes with cellular infiltration of the underlying myocardium. The myocardium was normal except for a few small areas of round cell infiltration.

About 100 c.c. of yellow ascitic fluid were found in the peritoneal cavity.

Liver: The liver weighed 2350 grams and had a nutmeg appearance on section. Microscopically, there was marked chronic passive congestion with bile stasis.

Spleen: The spleen weighed 350 grams. On section it was dark and congested and showed 4 or 5 old and recent yellowish, white and red infarcts, the largest being 2 cm. in diameter. Microscopic examination showed a large area of massive infarction, with perisplenitis. The sinusoids outside this area were markedly dilated.

Kidneys: The right weighed 300 grams, the left 250 grams. The capsules stripped easily. There were numerous old scarred areas on their surfaces which appeared to be old cortical infarcts. Microscopically, many of the glomeruli were found to be completely obliterated. A few of the glomerular tufts exhibited focal necrosis with suggestive embolization by bacteria. In some areas there was marked thickening of the capsule with partial or complete atrophy of the tuft. One large vessel showed what appeared to be recanalization.

The stomach, pancreas, gall-bladder, testicles, prostate, epididymis, and adrenals were normal. Microscopically, the adrenal exhibited a cortical adenoma.

Intestines: The jejunum, ileum and colon showed numerous small areas of punctate hemorrhages many of which were hard and felt like shots. Microscopically, several sections through the intestinal wall revealed thrombi in the submucosal vessels which probably represented non-bacterial embolization.

A left incarcerated inguinal hernia which contained a portion of sigmoid colon was present.

Bone: The vertebral bone marrow was dark red in color and microscopically revealed normal cellularity and constituents.

1/25 11 a.m. Sternal Marrow Puncture

Leukocytes 10000 per mm. Ratio 1 : 4.7
Nucleated erythrocytes 47000 per mm.
Megakaryocytes 20 per mm.

Differential—Polymorphonuclear leukocytes	0.5%
Myeloblasts	0.5%
Lymphocytes	16.0%
Monocytes	0.5%
Normoblasts	44.0%
Erythroblasts	33.5%
Megaloblasts	5.0%

Almost complete absence of granulocytic elements.
Numerous disintegrated cells are seen. The bone marrow thus exhibits a picture of agranulocytosis.

1/27 15 minutes after death 3:15 a.m.

Leukocytes 2200 per mm.
Nucleated erythrocytes 20000 per mm. Ratio 1:10

Differential—Polymorphonuclear leukocytes	0%
Myeloblasts	1%
Lymphocytes	49.0%
Monocytes	1.5%
Normoblasts	40.5%
Erythroblasts	7.0%
Megaloblasts	0.5%
Megakaryocytes	0.5%

Essentially similar to previous. Sternal marrow examination showing agranulocytosis.

Comment: The patient had subacute bacterial endocarditis and was given sulfapyridine as a preliminary to heparin therapy. In spite of this, the blood cultures remained positive. After a total of 89 grams of the drug had been given over a period of 17 days, granulocytopenia developed which went on to a complete agranulocytosis. The blood sulfapyridine was 5 mg. per cent when the granulocytopenia was found. This condition did not respond to transfusion and pentnucleotide as evidenced by the postmortem sternal marrow examination. It is difficult to say that the agranulocytic state was directly responsible for the patient's death, in view of his congestive heart failure. Postmortem examination disclosed subacute bacterial endocarditis, congestive heart failure, and a vertebral bone marrow which exhibited normal cellularity and constituents. The latter finding is not inconsistent with the agranulocytosis since the toxic process may selectively affect portions of the bone marrow. Thus, the section was probably made through a portion of marrow that either was not affected by the drug or had already regenerated.

Case 8. Leukopenia following sulfapyridine therapy. F. A., a 57-year-old white female, was admitted to the private surgical service of Dr. Martin Loeb on March 20, 1940 because of right upper quadrant pain of three days' duration. Physical examination was essentially negative except for slight rigidity on the right side of the abdomen and bilateral costovertebral tenderness. A roentgenogram of the gall-bladder showed failure of the organ to be visualized with the dye.

Laboratory examinations: The urine contained a trace of albumin and 8–10 white blood cells per high power field. The hemoglobin was 94 per cent (Sahli), the red blood cells 4,720,000 and the white blood cells 5,500 with 50 per cent polymorphonuclear leukocytes, 2 per cent band forms, 42 per cent lymphocytes and 6 per cent monocytes.

One week after admission, March 28, under spinal anesthesia, a cholecystectomy and prophylactic appendectomy were performed by Dr. Martin Loeb. At operation a diseased gall-bladder containing many stones was found.

Postoperatively the temperature averaged about 101° F., until April 6 when it rose to 104° F. At this time, signs of bronchopneumonia were found in the lower lobes of the lungs posteriorly. This was confirmed by roentgen-ray. A mouse inoculation of the sputum was negative for pneumococci. On April 5 the hemoglobin was 79 per cent (11.5 gm.), the red blood cells 4,100,000, and the white blood cells 5000, with 32 per cent polymorphonuclear leukocytes, 49 per cent band forms, 17 per

cent lymphocytes, and 2 per cent monocytes. Prior to the institution of sulfapyridine therapy at 3:30 p.m. on April 6, the hemoglobin was 69 per cent, and the white blood cells 4,300. Two grams of the drug were given as an initial dose and then one gram every four hours. By 7 a.m. April 7, 17 hours following the institution of the sulfapyridine therapy, the patient had had 6 grams of the drug. At 10 a.m. the drug was discontinued when a blood count revealed a fall in the hemoglobin to 60 per cent and in the white cells to 1700, with 4 per cent polymorphonuclear leukocytes, 32 per cent band forms, 30 per cent young forms, 30 per cent lymphocytes, and 14 per cent monocytes.

In the afternoon of the same day, the white count was 1425 with 2 per cent polymorphonuclear leukocytes, 40 per cent band forms, 20 per cent young forms, 22 per cent lymphocytes, and 10 per cent monocytes. A transfusion of 400 c.c. of whole blood was given immediately, and pentnucleotide (10 c.c. intramuscularly) was started and continued three times daily until April 13, by which time the patient had received a total of 170 c.c. The urine on April 8 revealed a faint trace of albumin and a negative benzidine reaction. Following the transfusion the patient improved rapidly. The hemoglobin and white cells rose, the latter on April 10 to 6,600 with polymorphonuclear leukocytes 62 per cent, band forms 10 per cent, lymphocytes 27 per cent, and monocytes 1 per cent, and then fell on April 12 to 5,400 with marked toxic granulation of the neutrophiles. (See table 7 for blood studies.) By April 13 the lungs were normal. The patient was discharged on April 24.

TABLE VII

Date	Hemoglobin % Sahli	Red Blood Cells	White Blood Cells	Polymorphonuclears	Band Forms	Young	Lymphocytes	Monocytes	Eosinophiles	Plasma Cells	Turck Cells
3/20	94	4,700,000	5,500	50	2		42	6			
4/5	79 (11.5 gm.)	4,100,000	5,500	32	49		17	2			
4/6	69 (10.1 gm.)		4,300								
3:30 p.m.				Sulfapyridine started							
4–7 a.m.	60		1,700	4	32	30	20	14			
4–7 p.m.			1,425	2	40	26	22	10			
4–8	84 (12.2 gm.)	4,500,000	2,800	45	22		24	4			
4/9	74 (10.7 gm.)		3,300	18	30	2	28	18	2		2
4/10	76 (11.9 gm.)	4,500,000	6,600	62	10		27	1			
4/11	70 (10.2 gm.)	3,500,000	5,500	55	18		18	7	2		
4/12	78 (11.3 gm.)	4,200,000	5,400	61	13		22	2	1	1 marked toxic granulation of neutrophiles.	

Comment: Though the patient had a leukopenia, she was given sulfapyridine for a bilateral bronchopneumonia. Seventeen hours following the institution of therapy, after 6 grams of the drug had been taken, a marked fall in the leukocytes had occurred. Accompanying this was a fall in the hemoglobin.

Discontinuance of the drug, a blood transfusion, and pentnucleotide stimulated the bone marrow, and within three days the number of leukocytes had risen to within normal limits.

This case is apparently the only one on record of the occurrence of a leukopenia following sulfapyridine after so short an interval (17 hours).

Discussion

Contrary to the experimental findings of Wein,[5] Mollitor and Robinson,[6] and Johannsen and St. George,[7] and the clinical observations of Whitby,[8] it has been shown by Marshall et al.[9] and Brown et al.[10] that sulfapyridine is more toxic than sulfanilamide in comparable dosages. Long et al.,[19] experimentally, and Reinhold et al.,[20] clinically, demonstrated that sulfathiazole is less toxic than sulfapyridine.

From January 1939 until February 1941, 344 patients received sulfanilamide, 49 neoprontosil, 8 sulfanilamide plus sulfapyridine, 4 sulfanilamide plus neoprontosil, and 2 sulfanilamide plus sulfathiazole in The Bronx Hospital (a general hospital of 300 beds). During this period there has been one case of agranulocytosis and one case of leukopenia following 45 and 4.3 grams of sulfanilamide respectively. This is an incidence of 0.58 per cent with respect to sulfanilamide alone. From the inception of sulfapyridine therapy in March 1939 until February 1941, 294 patients received this drug, and six sulfapyridine plus sulfathiazole. Agranulocytosis developed in one male and leukopenia in one female following 89 and 6 grams of sulfapyridine respectively, an incidence of 0.68 per cent. Ten patients received a combination of sulfapyridine plus neoprontosil during this latter period. In one patient leukopenia followed the use of 20 grams of sulfapyridine followed by 6 grams of neoprontosil, an incidence of 10 per cent. However, the white count fell following the discontinuance of the sulfapyridine; the fall was hastened during the administration of the neoprontosil and reached its maximum after this drug was discontinued. Fifty-one patients received sulfathiazole between July 1940 and February 1941. None of these patients exhibited a toxic effect on the myeloid elements.

The sulfonamides depress the function of the bone marrow and apparently act mainly by arresting the maturation of the leukopoietic elements.[11] The erythroblastic elements may also be affected. Arrest of maturation, however, does not fully explain the rapid disappearance of the circulating leukocytes. In acute hemolytic anemia produced by the ingestion of sulfanilamide, most authorities agree that the rapid fall of the erythrocytes and hemoglobin is due to a direct toxic effect of the drug on the circulating red blood cells. The few postmortem observations in this condition have revealed a hyperplastic marrow such as occurs in response to peripheral blood destruction. One may, therefore, postulate that the rapid disappearance of the leukocytes from the peripheral blood may be due in part also to a direct toxic action of the sulfonamides on these cells. The damage to the bone marrow may become manifest as early as one day after administration of the drug, or as late as 10 days after its discontinuance. (Briggs in one of his cases reports a granulopenia as late as 10 days after therapy was stopped.[12])

The total dosage, not the blood concentration of the drug, is probably the important factor in producing granulocytopenia. With sulfapyridine there has been as high a blood concentration as 18 mg. per cent without a deleterious effect and as low as 5.7 mg. per cent with granulocytopenia. Apparently an idiosyncrasy to the drug must exist before the effect on the bone marrow becomes evident. One of us (M.S.) has given a patient with subacute bacterial endocarditis 104 grams of neoprontosil in a period of 21 days, followed by 335 grams of sulfapyridine in the next 98 days. Another patient with the same disease received 21 grams of neoprontosil in a period of 10 days and 138 grams of sulfapyridine in the succeeding 27 days without any effect on the bone marrow or the disease itself. In the majority of the cases reported where agranulocytosis followed sulfapyridine, the dosage was above 50 grams, with a range of 18–95 grams.[13, 14] For agranulocytosis following sulfanilamide, the dosage has been between 40–50 grams with a range of 15–90 grams.[15, 16] In our series of cases leukopenia followed the ingestion of 65 grains (4.3 grams) of sulfanilamide in one case, and 6 grams of sulfapyridine in another. (The lowest dosage previously reported for a leukopenia following sulfapyridine was 6 grams.[17]) In three of the cases of agranulocytosis about 4 grams of sulfanilamide or sulfapyridine plus neoprontosil were taken. Sutherland[18] warns that quantities over 50 grams may be dangerous to patients who are already suffering from a disease which causes some destruction of the red cells. This statement should be modified. Much lower dosages, as pointed out above, can be just as dangerous. It also should be emphasized that leukopenia or agranulocytosis, just as hemolytic anemia or toxic hepatitis, may appear within 24 hours of the inception of sulfonamide therapy.

The frequency and seriousness of this complication may be surmised from the finding that in the borough of The Bronx, with a population of about 1,600,000, there were 12 deaths (practically all the cases were due to sulfanilamide) from agranulocytosis following the administration of the sulfonamides between 1938–1941.[21]

Summary and Conclusions

Six cases illustrating the toxic effect of the sulfonamides on the myeloid elements have been presented. Three have been due to sulfanilamide, two to sulfapyridine, and one to a combination of sulfapyridine plus neoprontosil.

Two cases of agranulocytosis followed the use of 4 and 45 grams of sulfanilamide given over a period of one and 21 days respectively. The patients did not respond to therapy and apparently died of the blood dyscrasia. One case of leukopenia developed after 65 grains (4.3 grams) of sulfanilamide given over a period of 24 hours.

Following sulfapyridine therapy, one patient developed a leukopenia after the ingestion of 6 grams over a period of 17 hours. In another patient, 89 grams of the drug taken over 17 days resulted in agranulocytosis. This

condition did not respond to therapy and apparently hastened the patient's demise.

Twenty grams of sulfapyridine plus six grams of neoprontosil taken over a period of 14 days, caused a leukopenia in another patient.

Two probable cases of agranulocytosis following sulfanilamide and neoprontosil therapy have also been presented. Both patients received about 3.5 grams of the two drugs. One of the patients expired and the other recovered.

From January 1939 to February 1941, 768 patients received sulfanilamide and its related compounds in The Bronx Hospital. Five exhibited a toxic effect on the myeloid elements, an incidence of 0.65 per cent. (Cases having received the drug before entry to the hospital are not included in the statistics.*)

Certain conclusions may be drawn from the cases presented.

We are dealing with drugs that have a definite toxic effect on the bone marrow, hence they should be used only when there is a definite indication. Promiscuous use for minor ailments, such as mild respiratory infections, tonsillitis, grippes, etc., is to be condemned.

Frequent blood examinations should be done not only while the drug is being given, but for 5–10 days after it has been discontinued.

The dosage of the drug, not the blood concentration, is probably the factor that determines whether a toxic manifestation will occur in a susceptible individual.

Although a small dose may cause leukopenia or a fatal agranulocytosis (4 grams in two of our cases), these toxic effects on the bone marrow usually manifest themselves after prolonged use, especially in instances where the disease itself has a deleterious effect upon the hemopoietic system.

In view of the incidence of the more severe manifestations of the sulfonamides, we feel that one is seldom justified in using these drugs prophylactically.

We wish to thank the physicians on the staff for permission to publish their cases and Dr. I. Rothstein who did the sternal punctures and blood studies on these cases.

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* During this same period there were two cases of acute hemolytic anemia; one, in a child, followed the use of sulfanilamide, and the other resulted from therapy with sulfathiazole in an adult. This is an incidence of 0.29 per cent and 2 per cent for sulfanilamide and sulfathiazole respectively, or a total incidence of 0.26 per cent. These figures are in marked contrast to the 1.6 per cent for sulfanilamide, 0.6 per cent for sulfapyridine, and 0.0 per cent for sulfathiazole reported from the Johns Hopkins Hospital by Long and his associates (Jr. Am. Med. Assoc., 1940, cxv, 364–368). Their total incidence for the sulfonamides was 1.2 per cent. However, as a greater number of patients continue to receive these drugs the incidence will fall further; and it is not amiss to say that the final incidence of the acute toxic effects on the blood elements will probably stabilize itself at under 0.5 per cent.

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THE RESPONSIBILITY OF THE HOSPITAL STAFF IN GRADUATE MEDICAL EDUCATION *

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It is a noteworthy fact that graduate medical education has grown in interest to the extent that responsibility for its careful planning and most effective application is now one of the foremost problems of the medical profession. The demand that educational opportunities be provided for all graduates is an equal partner with the need of making them want them and use them when they are provided. Practice, general and special, need not be criticised for this. For the progress in clinical medicine and in the related basic medical sciences is marching ahead with a rapidity overwhelming to the man who is very busy or otherwise isolated from easy knowledge of the advances.

Life in medicine is a great progressive program of education, in which our ignorance is being constantly revealed to us to our discomfort. As long as no callus of indifference forms to protect us, this discomfort will stir us to further action and prove our safety in the end. A satisfaction with what we have, a lack of desire for more, and little or no interest in the new cannot be overcome by the provision of opportunity alone.

The need of further instruction grows, as the decades dissipate the certainty of things which seemed to characterize the earlier years. These facts make right and proper the plans of continued medical education, now in the minds of so many, and at this time being put to trial in widely separated areas of this country. Further, any outgiving way of living, such as the practice of medicine, requires well planned and accessible means of refreshing. Graduate medical education must furnish this as part of what is best in the quality of life in medicine, in a manner, too, which shall redound to the credit of the participating doctor in the eyes of his patient, instead of criticism of him; shall label him as progressive and up-to-date in his community, instead of inadequate; and shall create in him a desire for the opportunity, even a feeling that he cannot afford to miss it, instead of one of satisfaction with what he already knows.

Out of this set-up grows the vision that we are participating in the total picture of life in medicine as one broad sweep of educational effort, taking in and giving out, from medical school days to later years—something no one is ever free of. Primarily, medical schools should be said to have succeeded when they send out an individual as a well trained student, implying the need of continuing education, rather than as a trained graduate. The idea of studies completed cannot enter, except as a mile-stone of time and accomplishment is recognized and then passed by.

* Read at the Boston meeting of the American College of Physicians, April 21, 1941.

If the seeds of enjoyment of learning have been sown, and the more or less insatiable demand and search for the truth are there, one finds the opportunity to satisfy it present in every hour and every day, and with every patient.

If, in turn, one is ambitious to teach and has a real love of teaching, he finds the opportunity every day of his life, whether it be to his patient, his patient's family, the nurse, the student, the industrial executive, his own family at home, or medical students, interns, staff members or older colleagues. The opportunity challenges him every day. It fairly envelops the man in medicine today. The response depends upon him, his natural equipment, upon the examples that have been set him, and his earlier training.

These facts build the picture of medicine as a huge program which is educational by natural evolution. Medicine must expect of its graduate this dual rôle of student and teacher. It should be firmly engrafted in his purposes before graduation. If he is a good student, he has the first point in making him a good teacher.

One must continually seek the truth, and then share it with his colleagues and others, if to their advantage. In medicine it is to our credit to covet the knowledge and skill of the other fellow and work until we get them.

The trend today in all professions, not medicine alone, is toward a conversion of what is traditionally acknowledged as a need for constant study, into real action in the form of search for opportunities to learn and if possible by some reasonable method of concentrated devotion of time and effort. President Ruthven of the University of Michigan has recently pointed out that the universities in recognizing this to be a fact have reached out to meet what they consider a laudable restlessness and urge among their own graduates. Now they are ready to do so for as many of their related community groups as they can serve.

As early as 1934, " this expansion of interest in acquiring new knowledge " was referred to as " part of a world-wide renaissance in adult education which is permeating all phases of life."

Most revealing is the surprising amount of literature upon the subject of graduate medical education. For three decades this has been appearing increasingly. No one at this stage can have a very original idea or plan, so many and varied and thorough are the articles on record. One can express the situation only as he speaks of the experiences of innumerable enthusiasts, men, and groups of men, who have given themselves to the project.

With state and county societies taking up the cudgel, besides here and there conspicuously an interested leader in medicine, certain national associations and a number of foundations have found it a field for surveys, reports, planning and experimenting. All of these merit careful study, especially the plans of certain foundations to improve medical practice in local areas. Then, too, awareness is necessary, because the already established mechanisms and relationships should not be upset too radically. Regulatory plans

do not supply the need. The ideal is to inject into what is going on, the spirit of renewed study and sacrifice to make increased knowledge and skill available to patients.

The opinion has been expressed that this literature is not read by the profession in general. Anyone forced to review the literature on graduate medical education which has been appearing during the 40 years of this century will be amply repaid. For this review gives substantial foundation and background to any thoughts expressed today, to the suggestions and convictions or results of experiments which furnish answers to this whole problem.

The field least adequately handled, or even considered, in relation to graduate medical education, is that expressed by the title of this paper, the responsibility of the hospital staff.

Medical schools and universities must be the fountain-head for matters pedagogical in medicine. Those who are devoting their lives to teaching must be respected for their greater knowledge in the educational field, even though there is a group who are more devoted to the content of their special field than they are to ways and means, methods, and values involved in the general problems of teaching.

The interest and time of medical school and university hospital staffs and their available funds are said to be taken up with the responsibilities of undergraduate medical education, with the exception that graduates of promise are carried along in opportunities of advanced study and research. This is the group out of which the future teachers and university leaders come. In spite of their full schedules, the majority of university hospitals throughout the country are now giving medical courses for postgraduates at certain times of the year.

In one western state the success of the plan was reported not only in the advantages to the practitioner and the practice of medicine, but it was said the "cloistered professor was given a chance to become acquainted with the general practitioner and his problems," the inference being that his teaching improved along practical lines, more in keeping with the needs of the man in practice.

Much has been said of the university hospital in this connection, but the large general hospital, the community hospital with staff large enough to be balanced, has its own particular field of work to perform. Because it is not a university hospital, it is often called a non-teaching hospital. Many influences in the last 25 years, external and internal, have developed teaching in it as a necessary part of staff training, of clinical programs and of bedside and laboratory work. The reference to it as a non-teaching hospital today means that it is not a university hospital in close relation to the medical school. The staff of the hospital values relationship with the university and medical school, realizing that what the latter prizes most in standards and qualifications, the hospital staff wants most to have. One who has lived

through the life-time of such an institution from its beginning 26 years ago to date, can testify to the high purposes and ideals behind its inception and growth, built as a community hospital, organized for service to a city, with the emphasis on standards of care, teaching of staff, and research, as being those influences which interact to produce the most progressive work, the greatest happiness in the work and the best results. If such a hospital is not equipped and qualified to share in some way in the needed graduate teaching, then the first responsibility is to convert it so that it may do so and can be said to have a professedly teaching staff.

Let us see what such a hospital staff is doing today to justify what has been said. Very few staffs of 150 or more are without a nucleus of members who have taught in medical schools in earlier years. They will always have the love of teaching in their hearts. They still have the urge to demonstrate clinical examples somewhat in the happy style exemplified by Osler, or to make an operating pavilion somewhat as impressive as did Halsted, or even to illustrate a pathological demonstration somewhat as vividly as did Welch.

There is little need for external influences to lead such a group to study and to apply the best methods of teaching an intern curriculum; to make maximum use of clinical material for the training of individual members; to pick up with renewed enthusiasm the emphasis upon basic medical sciences in seminars, in special group meetings, in personal thinking and in the analysis of individual cases.

It should go on record that such an institutional staff includes teachers who are keeping in close touch with their colleagues in academic circles and profiting by the opportunity. Such a hospital chooses for its intern the graduate who wants to learn, and then strives in teaching him to develop further his teaching qualities first brought to the fore in his medical school days. The internship thus becomes the second phase of this student-teacher life in medicine.

The activities of such a hospital staff in graduate medical education are both intramural and extramural. The intramural program is built about the staff in training, men who remain one to five years.

In these years, the aim is to develop a spirit in the man and a relationship in the hospital which will form the basis of the extramural program later. In the man, it is the spirit of study and of search for the truth; in the hospital, the providing of opportunities.

Again we should like to emphasize the continuous, educational character of life in medicine, wherein the pre-medical and medical school days form the first phase; the intern and resident years form the second phase; and the life-long era of practice of medicine, general or special, forms the third phase.

The possibilities of continued medical education through the years after graduation are first determined by the type of applicants admitted to medi-

cal schools. During the years of instruction in basic medical sciences and clinical subjects, medical schools are even more responsible for the definition of the limits of later education. The quality of the teaching and of the examples set enables some schools to send out men with the vision of continual striving and study toward that goal of perfection which is never reached; whereas from others the graduates are more inclined to be guided by the one idea of getting to practice by the shortest possible route. Those qualities must be part of him at graduation which make him enjoy the life of a student and look forward with the expectation of living it out in the next two phases of his medical work, in the hospital and in his practice. This is a crucial point for graduate medical education which needs more consideration and pressure. Otherwise it is a despairing task to try to develop this spirit later. The exception may be in those men who seem to find themselves and life's values so much more clearly in the years of hospital training. This usually does not arrive during intern year. It is an experience peculiarly of the third year, during the residency, and some evidence suggests it is related to the way in which responsibilities are placed upon him at this time. Osler says: "To his five senses he must add two more—the sense of responsibility and the sense of proportion." These are frequently acquired at this time, and a new man emerges.

So the hospital shares with the medical school the responsibility for nurturing and developing these factors, upon which it is fair to believe postgraduate medical education depends for its successful building.

If the need of the medical school phase is fulfilled, the challenge of the next period must be accepted by all hospitals that appoint young graduates to their staffs, because they are the core of their intramural, teaching activities.

Our experience is clear on this point—if these qualities of continued study and ability to share and impart knowledge, what we have called in this paper the student-teacher qualities, if these are further nourished and kept alive during his year or years of hospital internship and residency, we have every reason to expect this man to carry on as a serious participant in graduate medical education in the years of practice, whether general or special, wherever he is, in the larger city or in the relatively isolated, rural districts.

The how of this accomplishment during intern and resident years is not nearly as important as the spirit behind the how, the adherence to this principle and to this objective, in all the various plans in use for the training of interns and younger staff men.

Throughout the first year, demonstrations and discussions, and emphatically not didactic lectures, are the program. In the spirit of the teaching, "there is no appreciable difference between the teacher and the taught—both are in the same class, the one a little more advanced than the other." The interns are made familiar with the laboratory methods in vogue in the

hospital; the history taking procedures and general and special examinations used; the diagnostic and therapeutic technics employed; the business of floor administration; emergency states and their handling; the special classes of medications found most useful; the place of physical therapy; medical ethics, customs and courtesies; and the medical economics of the institution and of practice. Procedures are followed through so that it is known that each man has had each experience at least once under supervision. In all clinics, section meetings, special seminars, and so on, the junior men are the focus of teaching. Residents learn much by supervising and teaching interns. Each man is expected to create his own record of his instruction and experience. In this way he is very possessive of his knowledge. It is part of him. Whereas if typed outlines and a syllabus are issued to him, he is apt to store them away in a top drawer without knowing their contents and yet comfort himself with the thought he can get them again when the need arises. The aim is to stimulate the need of personal effort to get and to have and even share with others. For this is the very essence of the habits of continuance.

Osler has summed up the picture in his essay, The Student Life: "the hardest conviction to get into the mind of a beginner is that the education upon which he is engaged is not a college course, not a medical course, but a life course, for which the work of a few years under teachers is but a preparation."

It has been said: "While many things are studied, few are studied thoroughly. Men will not take time to get to the heart of a matter. After all, concentration is the price the modern student pays for success."

This is the challenge of the resident years and by making assignments to smaller groups, subsections with more limited fields, after intern year, they have the association with men who show them what it is to delve deeper into clearer understanding of backgrounds and underlying conditions. When clinical medicine, so easily handled in the main without it, has the door opened constantly to the values of the underlying anatomical, physiological and biochemical values, understanding replaces strained memory, and the possibilities of complacency dominating the spirit are dispelled.

Most fortunate are the general hospital staffs that prize a close relationship to a medical school and university. Our residents and younger assistants may register in the graduate department of the University of Michigan and accumulate credits for advanced degrees thereby, while the major part of their work is research in the hospital leading to a final thesis. By this plan, recognition is given to the quality of work of the staff as well as its ability to teach. It is beneficial for both student and hospital.

There is no doubt the residents bring something back from the university which contributes a certain academic character to the conduct of medicine—is stimulating, is making a better clinician of the man, and enhances the efforts of the staff in general. It is by all means the advisable plan, and it

would be a great stimulus and a step ahead if universities would make such hospital staffs or selected members of it an allied, second line of resource in the great field of graduate medical education. For such men in one hospital have already taken over the second phase of training of enough men from different medical schools to approximate (if they all came from one school) one-quarter of the annual graduates of that school. With such hospitals now carrying that responsibility in the training of interns and residents, it cannot be denied that they are playing a large part in the continuance of education of the graduates of all medical schools. Certificates of service plus university credits under this plan will represent much more than just necessary time put in.

The extramural activities of the hospital staff in this field in the State of Michigan are fortunate to be under the wise and untiring leadership of Dr. James D. Bruce, now President of the American College of Physicians. With very evident enthusiasm, university and medical school faculties, members of the state and county societies, and especially of the hospital staffs have joined to provide useful courses in teaching centers, as well as to bring education along practical lines to the man who cannot afford in time or money to go any distance to get it. Dr. Bruce has furnished vision as a pioneer and unusual organizing ability to bring these plans to successful accomplishment.

We have referred to the third phase of the continued medical education as that coming during the years of practice, general or special. A plan has evolved from the impressions gained during a reunion of ex-staff members of the hospital. The surprising spirit of enthusiasm and regard which brought men back from considerable distances, and the enjoyment of sharing the institution and its work again with them showed the existence of an attachment that immediately suggested an unfulfilled obligation on the part of the hospital staff.

Since then, the plan has been unfolding which would cover for a lifetime much of the problem of graduate medical education for an increasing number of doctors in practice.

With 50 or 60 men leaving the staff each year, after one to three or five years' service, the effort has been to tie in with them in their new fields sufficiently to keep alive their friendships with the staff and their feeling that the hospital is a continued source of supply to them even in their absence. This has had nothing to do with the reference of cases, because these men have scattered over the widest areas of the nation and world. Special efforts are made to send them copies of detailed reports of clinics; copies of literature; reviews of section meetings; case reports illustrating new advances in any line, especially therapy; autopsy reports; case reports brought up in clinical pathological conferences; reports brought back from meetings attended; and specially prepared material, if of special benefit to them.

A perfect stream may go forth from men whom they know and who in turn know their needs and speak their language.

This is capped by devoting a weekend, once a year, maybe twice, to a program wherein the current work in the hospital is shared and these men are lived with on a basis of friendship and needs. This plan has stirred the enthusiasm of the hospital staff. It has met a fine reaction on the part of the ex-staff members. The opportunities are supplied in a manner which is natural and consistent with the self-respect of the doctor and his standing in the community. Instruction comes from men who know him on a basis already established, men who are aware of the spark, the interest, the hunger, the need of this particular individual. The maximum can be accomplished in this personalized way to prevent mental, moral and physical death of the individual. Each hospital in turn can have the realization, that, in this great plan of continued medical education, it is taking its share of responsibility, and most peculiarly fulfilling an obligation that is its very own.

CASE REPORTS

THROMBOCYTOPENIC PURPURA ASSOCIATED WITH DISCOID LUPUS ERYTHEMATOSUS AND RENAL GLOMERULAR CHANGES *

By Morton H. Edelman, M.D., *New York, N. Y.*

The occurrence of thrombocytopenia associated with lupus erythematosus has been referred to by Templeton,[1] Lyon,[2] Baehr, Klemperer and Schifrin,[3] Ginzler and Fox,[4] Keil,[5] and others. However, it had been previously observed by Libman and Sachs [6] in the second of the four cases, which they reported in 1924 and which for want of a better name, they called atypical verrucous endocarditis. Up to the present thrombocytopenia and the accompanying thrombocytopenic purpura have been considered by many one of the visceral or systemic manifestations of the disseminated form of lupus erythematosus. Further, the chronic fixed variety of lupus erythematosus has been considered non-fatal unless an acute exacerbation with dissemination of skin lesions occurs. It is, therefore, of special interest that the present case report with necropsy findings presents an instance of the co-existence of acute thrombocytopenic purpura, discoid lupus erythematosus, and renal glomerular changes.

Case Report

Clinical History: J. R., a 49-year-old salesman, entered the hospital October 24, 1939 acutely ill. He had begun to suffer from thrombo-angiitis obliterans of the lower extremities at the age of 34. The chief symptoms had been cramps in the legs and feet, with swelling of the ankles, particularly in the spring and fall. Treatment by physical methods and exercises had been followed in recent years by disappearance of many of the complaints referable to the lower extremities. Appendectomy was performed at the age of 42. A chronic skin condition of the face was known to have been present for two years.

In September 1939, he began to experience frequent epistaxis, slight bleeding from the ears, ecchymoses of the arms and legs, soon followed by severe frontal headaches, dyspnea on exertion with palpitation, and weakness. Then for 10 days there was repeated diarrhea with tarry stools and hematemesis, followed by progressive weakness, dizziness, and pallor. The diet had been poor in meat, bread and butter and excessive in spicy foods.

Physical Examination: On admission the temperature was 100° F., pulse 108 per minute, respirations 20 per minute, systolic blood pressure 120 and diastolic 70 mm. of Hg. The patient appeared extremely ill, pale, and dehydrated. There was dyspnea at rest and marked restlessness. There were many small and large ecchymotic spots over both arms and legs.

Over the temporal and malar areas of both sides of the face were patches of

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From the Department of Medicine, Jewish Hospital, Brooklyn, New York, Service of Dr. E. L. Shlevin.

typical discoid lupus erythematosus. These areas were reddish scars, denuded of hair, infiltrated, depressed, atrophic, with adherent scales and many patent follicles.

Ophthalmoscopic examination showed pallor of the optic discs but no other abnormalities. The lungs were clear. The heart was not enlarged to percussion. The heart sounds were of fair quality and regular in rhythm. An apical systolic murmur was heard. On abdominal examination the liver and spleen were not palpable. The pulsations of the dorsalis pedis vessels were absent but the pulsations of both posterior tibial vessels were fairly strong.

Course in the Hospital: October 29, 1940: Fever ranged between 99° and 102.4° F. Small amount of blood streaking found in the sputum and in the nasal discharge.

TABLE I

Laboratory Findings on Admission—October 24, 1940

Hematological	Chemical Examination of the Blood	Urine
Hemoglobin—37%	Urea nitrogen—22.0 mg. %	Specific gravity—1.010
Erythrocytes—2,170,000	Sugar—88.0 mg. %	Albumin—faint trace
Leukocytes—7,500	Fibrinogen—436 mg. %	Sugar—absent
Polymorphonuclear neutrophiles—54%	Calcium—8.8 mg. %	
Band forms—18%	Phosphorus—3.9 mg. %	Microscopic—occasional red blood cell
Lymphocytes—22%	Total protein—5.19 gm. %	
Monocytes—3%	Albumin—3.45 gm. %	
Eosinophiles—2%	Globulin—1.7 gm. %	
Basophiles—1%	A/G Ratio—1.98	
Platelets—30,000		
Bleeding time—3½ min.		
Clotting time—8½ min.		
Reticulocytes—9%		
Prothrombin time—normal		
Fragility test—normal		
Bone marrow—absence of megakaryocytes *		
Blood Wassermann test negative; blood culture sterile; sedimentation rate 70 mm./hr. (Westergren)		

* Examination of the bone marrow on postmortem study showed adequate numbers of megakaryocytes. A possible explanation for this may be that on sternal puncture a specimen from a very limited area is aspirated and the findings may not be a true representation of all the bone marrow elements.

TABLE II

Date	HGB.	RBC.	WBC.	PMN.	Band	Lymph.	Mono.	Eos.	Basophiles
10–24–40	37%	2.17	7500	54	18	22	3	2	1
10–27–40	37%	1.84	7200	66	10	24	0	0	0
10–28–40	40%	2.64	6625						
10–30–40	37%	2.04	8800						
11– 2–40	34%	1.85							
11– 5–40	37%	1.56							
11–10–40	37%	2.7	8000	50	17	26	6	1	0
11–15–40	25%	1.77							

TABLE III

Date	Bleeding Time	Clotting Time	Platelets	Reticulocytes
10–24–40	3½ minutes	8½ minutes	30,000	
10–26–40	6 minutes			
10–27–40	6 minutes	8 minutes	30,000	9%
11– 5–40				5.6%
11–17–40	2½ minutes		36,000	

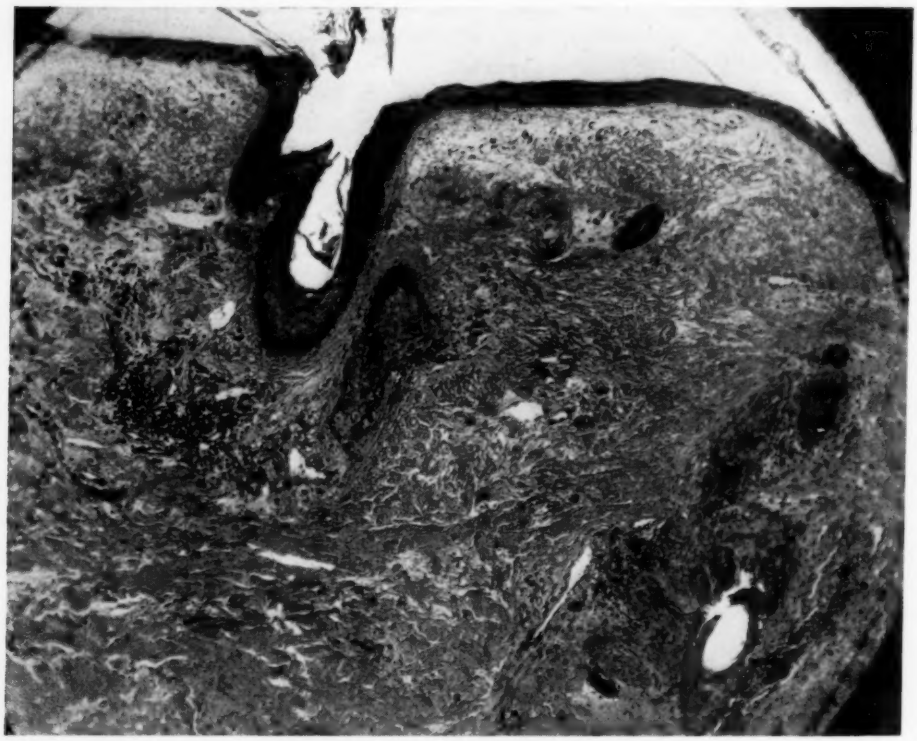

FIG. 1. Photomicrograph of section of skin taken from area of discoid lupus erythematosus of the face.

November 3, 1940: Several episodes of epistaxis occurred. Temperature ranged between 98.6° and 103° F. Fundus examination showed a few linear hemorrhages. There were numerous ecchymotic spots over the skin.

November 5, 1940: Patient appeared weaker; bleeding from nose and gastrointestinal tract was increased. The platelet count was 30,000 per cm., the reticulocytes were 5.6 per cent. Ecchymotic spots appeared on lips, buccal mucous membranes, and pharynx.

November 6, 1940: Excision of specimen of skin from area of discoid lupus erythematosus on right temporal region of face showed the following on histological examination:

"One surface is corrugated and is covered by a narrow band of stratified squamous epithelium with keratinizing superficial layers and short blunt rete pegs. The epidermis is flattened out, and the papillae have for the most part disappeared. The vessels within the papillae are likewise few in number. The lymphatics are distended. In the deeper portions, there are focal areas in which there is an infiltration by small round cells, and large mononuclear cells, with occasional plasma cells. Some of these are seen also about blood vessels. There is marked edema of the connective tissue both superficial and deep, and the tissue here has a somewhat basophilic tint. With elastic stain there is marked swelling, fragmentation and clumping of the elastic tissue. Diagnosis: Lupus erythematosus." (Dr. D. M. Grayzel and Dr. D. L. Satenstein.)

November 9, 1940: Ophthalmoscopic examination: "Media clear; fundi presented general pallor of the optic discs. Disc margins were clear except where obscured by retinal hemorrhages. Veins were tortuous, full and deeply colored. Throughout both fundi there were large, purplish colored linear hemorrhages and small circular whitish exudates; both hemorrhages and exudates were perivascular." (Dr. J. Levitt)

November 11, 1940: Patient vomited 500 c.c. dark brown material and small clots of blood. Pulse was weak and rapid. Abdomen was full but the spleen was not palpable. During the ensuing week there was continued intestinal bleeding, fresh and old blood found in the mouth, extreme weakness, rapid, shallow respirations, thready pulse, pallor, lethargy, tenderness and distention of the abdomen. Heart sounds were distant and regular in rhythm.

November 14 to 19, 1940:

Blood Pressure	110/64 mm. mercury
Temperature	98.6° to 103° F.
Pulse	80 to 160 per minute
Respirations	20 to 40 per minute

Nov. 15, 1940: Urine examination revealed no abnormalities (specific gravity 1.018). All previous urine examinations between October 31, and November 15, 1940, were normal, the specific gravity ranging between the values of 1.014 and 1.020. The exception was the admission urine specimen which on examination revealed a faint trace of albumin and an occasional red blood cell.

There was onset of hiccoughing which continued periodically until death. The vomitus became grayish. Tongue was covered with old blood. Sclerae became subicteric. Both lungs were clear radiographically.

November 19, 1940: Patient found gasping for breath. Pulse and heart sounds became imperceptible and breathing ceased at 7:30 p.m.

Postmortem Findings

Macroscopic: The body was that of a well developed, poorly nourished, white adult male. The skin was pale and there were a few fresh purpuric spots over the abdomen.

There were several small areas of hemorrhage beneath the endocardium of the right atrium and ventricle of the heart. The valve leaflets were thin and delicate. The anterior descending branch of the left coronary artery was tortuous and its distal third could not be traced. There was no evidence of bronchopneumonia. The stomach and intestines were distended with dark blood. There were a few shallow, irregular ulcers in the stomach. There were numerous, irregular, shallow mucosal defects similar to those in the stomach throughout the entire extent of the small bowel. The colon and rectum contained shallow ulcers similar to those in the stomach and small intestines. The gall-bladder contained a solitary, mixed mulberry calculus. The kidneys showed a finely and coarsely granular pale pink surface and were usual in size.

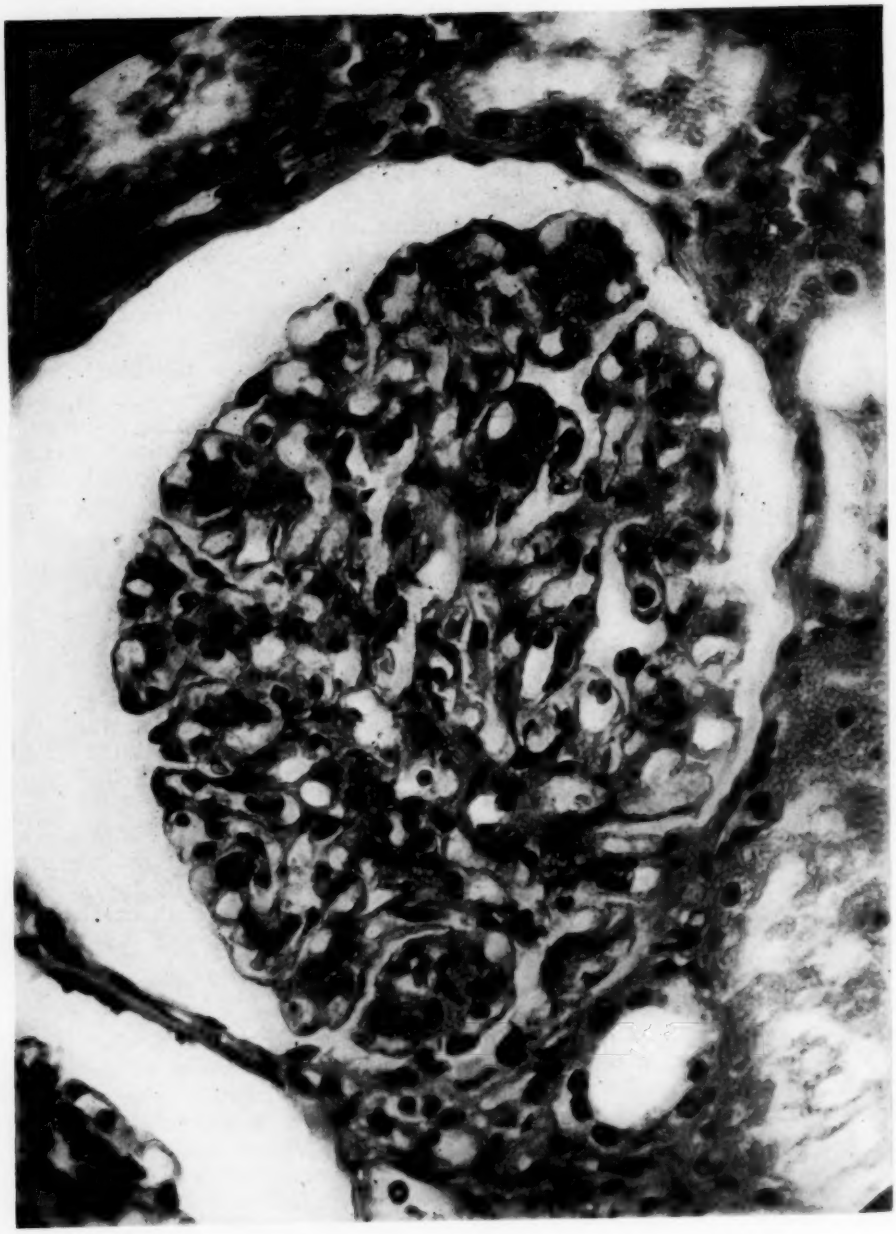

FIG. 2. Photomicrograph (× 500 magnification) of a glomerulus showing irregular thickening of the basement membrane and focal endothelial proliferation.

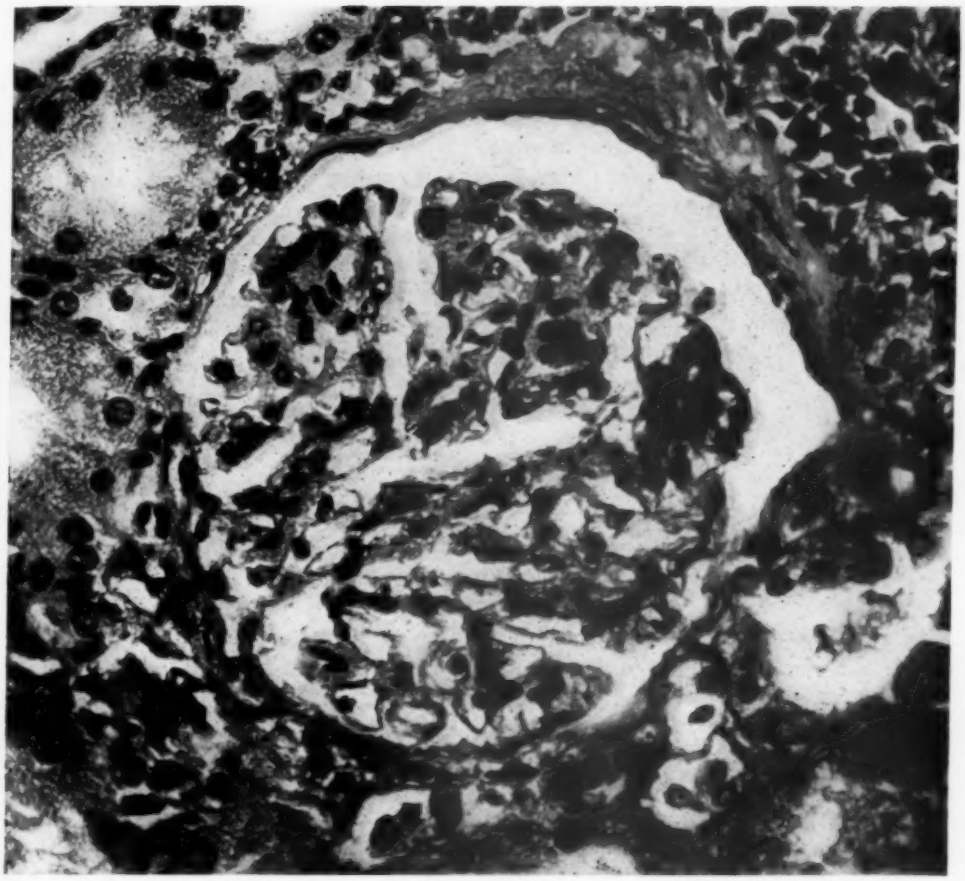

FIG. 3. Photomicrograph (× 600 magnification) of glomerulus showing in areas thickening of the basement membrane and endothelial proliferation.

The spleen was slightly enlarged. The abdominal lymph nodes were enlarged, soft and discrete.

Microscopic: The wall of the right coronary artery was thickened and its lumen was filled with a canalized thrombus. Two vessels at a point beyond which it was not possible to trace the anterior descending branch of the left coronary artery, showed lumina with canalized thrombi. The myocardium showed scattered patches of fibrosis.

The aortic lymph nodes were loosely arranged and contained many large phagocytic and reticular cells.

In sections of the stomach that were taken, none of the ulcers that had been observed were found on microscopic examination. In the small intestine, the mucosa was missing in many places and was replaced by large masses of detritus, containing many small and large mononuclear cells, extending to the submucosa.

There were a few areas of necrosis in the liver and pancreas. There was some hyalinization of the arterioles in the spleen. The kidneys showed definite thickening of the basement membrane in many places resembling " wire-loop " lesions. In places there were evidences of proliferation of the endothelial cells of the glomerulus.

Summary of the Case

The patient, a man 49 years of age, suddenly developed an acute thrombocytopenic purpura. Discoid lupus erythematosus of the face was present and was verified histologically. The anemia was severe and the bleeding uncontrollable. No treatment that was attempted could check the rapidly fatal course of the disease. There was persistent elevation of temperature. The blood culture was sterile. The urine remained clear. The lungs were radiographically clear. There was no evidence of endocarditis. Death was due to hemorrhage and exhaustion.

Autopsy revealed numerous ecchymoses of the skin, the stomach and intestines distended with blood, the spleen slightly enlarged. The significant microscopic findings were in the kidney and consisted of thickening of the basement membrane in places resembling " wire loop " lesions and proliferation of the endothelial cells of the glomerulus.

Comment

It is impossible, with our present knowledge of the subject, to prove that the glomerular changes or the acute thrombocytopenic purpura in this case, are visceral manifestations of the discoid lupus erythematosus that was known to exist both on clinical and histological survey. Suffice it to say that both have been described with the disseminated variety of lupus erythematosus and have been considered part of the disease mainly because of the increasing number of cases in which each of the above findings has been observed. Both are important, because if the glomerular changes are visceral manifestations of discoid lupus erythematosus, then additional evidence is brought to bear that the fixed and the disseminated varieties of lupus erythematosus are merely morphologic variants. It is not completely agreed that this is so. Further, if the thrombocytopenic purpura is a manifestation of the discoid lesions that were found, it would necessarily indicate that visceral manifestations of a serious nature may occur with this variety of skin lesion. It has been repeatedly stated that patients with the chronic discoid lesions are not otherwise ill and do not die of the disease. It is well known that the discoid form may undergo acute exacerbation with a dissemination of skin lesions. The associated findings here reported, if they are not coincident, would imply that the discoid form may undergo an acute exacerbation with visceral changes without dissemination of skin lesions.

The renal changes, the so-called " wire loop " lesions, are described in a paper by Baehr, Klemperer, and Schifrin.[3] Stickney and Keith [7] recently reported that in 8 of 15 cases of disseminated lupus erythematosus there was no definite renal change except that seen terminally in debilitating diseases. The most definite lesion that they found was a proliferation of the endothelial cells of the glomerular capillaries, although hyaline thickening of the basement membrane was also frequently present. The arteries and arterioles were found to be normal in most of the cases. The glomerular alterations in the present case were not striking, but positive findings, as suggested by the report of Stickney and Keith, are of significance.

Conclusions

1. A case of acute thrombocytopenic purpura associated with discoid lupus erythematosus without dissemination of the cutaneous lesions is reported.

2. Renal changes consisting of thickening of the basement membrane in places resembling "wire-loop" lesions, and endothelial proliferation in the glomeruli were found at autopsy.

Thanks are expressed to Dr. M. Lederer for reviewing the paper and to Drs. E. L. Shlevin and A. Walzer and A. Davidson for their kind assistance.

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MYXEDEMA HEART; REPORT OF A CASE*

By Arthur M. Master, M.D., F.A.C.P., and Jenny Stricker, M.D.,
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The following case is reported because it presented all the typical findings of myxedema heart, which disappeared after thyroid treatment. In addition, the occurrence of pericardial effusion in myxedema heart and its bearing on the symptomatology of the disease will be discussed.

Case Report

History. B. S., a white female of 37, developed the clinical signs and symptoms of hyperthyroidism at the age of 27. The basal metabolic rate at that time was + 63 per cent. Following a subtotal thyroidectomy the patient did well until one year ago, when progressive weakness and fatigability became evident. Despite a normal blood count she was treated with liver and iron without relief of her symptoms. Two months prior to observation she had the grippe, which was followed by increased weakness and shortness of breath. She complained of precordial pressure at rest and particularly on exertion.

* Received for publication August 31, 1940.
From the Cardiographic Laboratory, The Mt. Sinai Hospital, New York City.

Examination. Physical examination revealed a well developed female. The skin was dry and showed definite loss of turgor. The thyroid gland was not palpable and the healed thyroidectomy scar was apparent. The apex beat was neither visible nor palpable and the heart sounds were of poor quality. The heart rate was 70 beats per minute and the blood pressure 98 mm. of Hg systolic and 70 diastolic. There was no evidence of congestive failure.

Fluoroscopy and the roentgenogram (figure 1) revealed a generally dilated, flabby heart which was enlarged to the right and left. The pulsations were definitely diminished and sluggish. This was also seen in the roentgenkymogram. The electrocardiogram (figure 1) showed low voltage of all the complexes and left axis deviation. The basal metabolic rate was — 19 per cent. This in conjunction with the other findings suggested the diagnosis of myxedema heart.

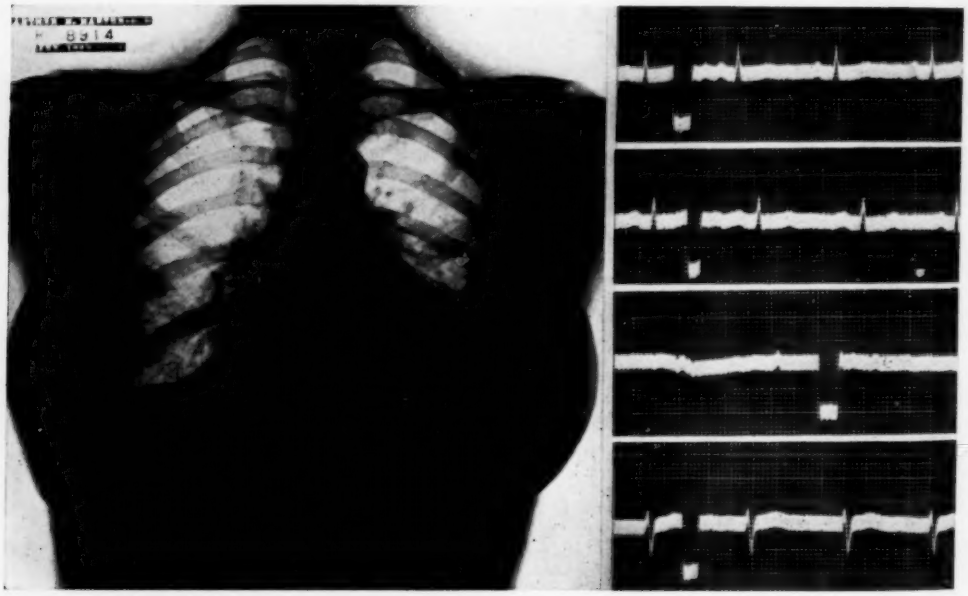

FIG. 1. Teleroentgenogram and electrocardiogram before thyroid treatment was begun. Basal metabolic rate — 19 per cent. Heart enlarged to the right and left (water bottle shape). The electrocardiogram shows low voltage of the QRS (4 mm.) and T-waves.

Clinical Course. Thyroid medication, 1 gr. daily, was instituted. After 15 days of this treatment the patient was subjectively improved; she was less tired and felt generally better, although there was no change in the basal metabolism or in the electrocardiogram. The thyroid dose was increased to 3 gr. daily and within a week the basal metabolism had risen to — 5 per cent and the blood pressure to 110/70, and the heart sounds were of better quality. Fluoroscopy and roentgenogram (figure 2) showed a definite decrease in the size of the heart, although it had not returned to normal; the cardiac pulsations were of larger amplitude. In the electrocardiogram (figure 2) the voltage of the QRS and T-waves had increased. The dose of thyroid was then reduced to 2 gr. daily to avoid the possible ill effects of overdosage. A week later the basal metabolic rate was — 4 per cent and the blood pressure 115/70. The electrocardiogram taken at this examination (figure 3) revealed all the deflections to be of normal voltage and on fluoroscopy the heart was of normal size; in fact it was a small heart (figure 3). The contractions were vigorous. Ten days later the patient

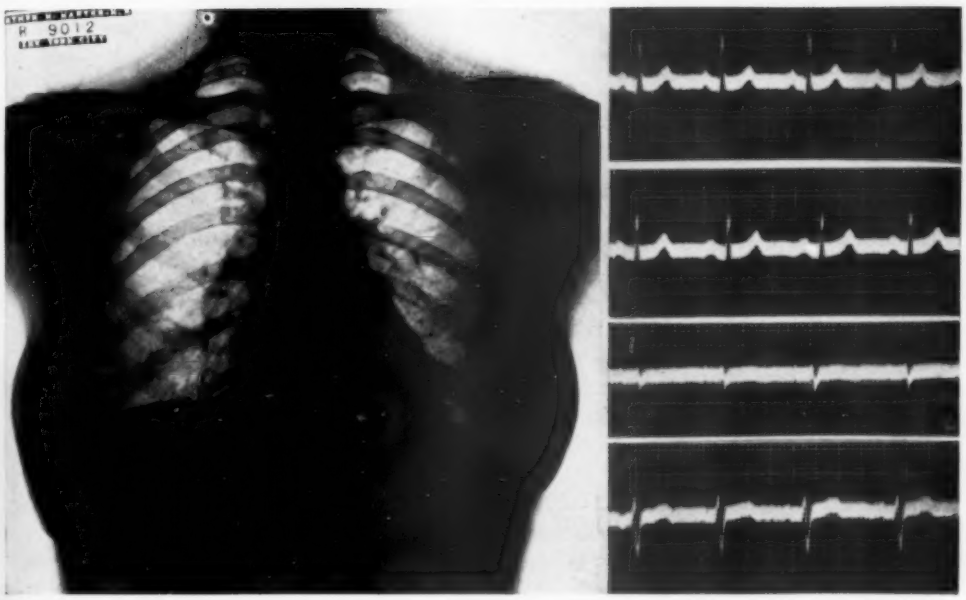

FIG. 2. After six weeks of thyroid medication. Basal metabolic rate —4 per cent. Teleroentgenogram shows decrease of the heart size. In the electrocardiogram there is an increase in the voltage of the QRS to 10 mm. The T-waves are of normal amplitude. There is a slight left axis deviation.

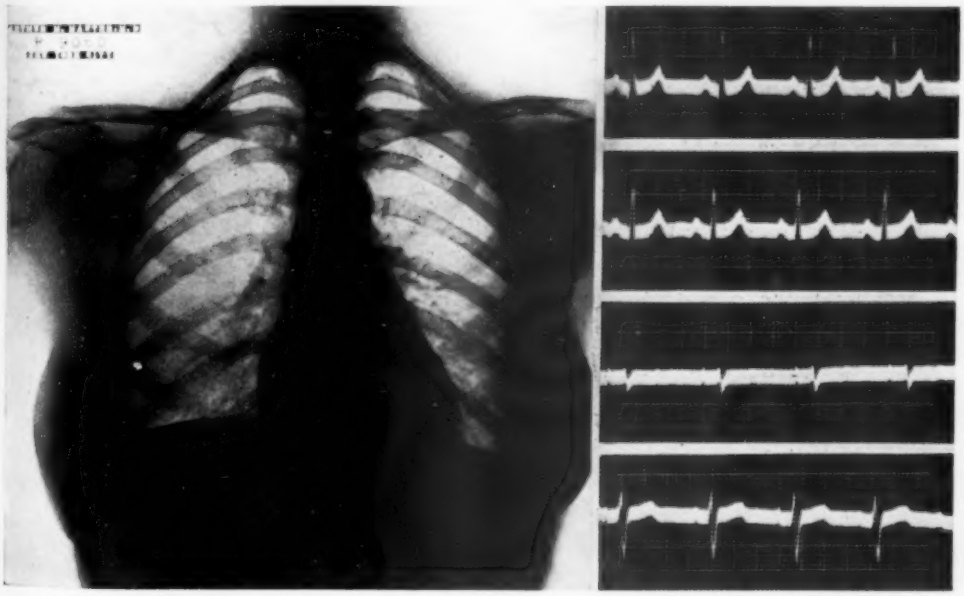

FIG. 3. After two months of thyroid medication. Basal metabolic rate + 2 per cent. The roentgenogram shows a heart of normal size, and the electrocardiogram a further increase in the voltage of the QRS and T-waves.

reported that she was much improved, was very active and complained no longer of any fatigue or weakness.

Comment

Although it is uncommon to find all the characteristic signs and laboratory evidences of myxedema heart in any single case, our patient was a classical example of this disease. Usually the basal metabolic rate in cases of myxedema is lower than in our patient, yet this diagnosis seems established by the rapid regression of cardiac enlargement and clinical and electrocardiographic improvement following thyroid therapy. Other cases of clinical myxedema with basal metabolic readings of —20 per cent have previously been reported.[1]

In 1918 Zondek [2] was the first to describe myxedema heart as a clinical entity. He reported four unusual cases which presented cardiac enlargement and sluggish cardiac movements accompanied by bradycardia and alterations in the electrocardiogram. He demonstrated the remarkable diminution in the heart size and the return to normal of the electrocardiogram following thyroid administration. Since his original communication ample corroborative evidence has accumulated to justify the term myxedema heart. Assman [3] and also Fahr [4] reported cases of myxedema heart upon which digitalis had no effect. However, when thyroid medication was instituted marked improvement of the myxedema with disappearance of the fluid due to "heart failure" was noted. This is further evidence of an endocrine factor.

The myxedema heart presents a characteristic roentgenoscopic picture. It is triangular in shape and its silhouette bears a striking resemblance to a water bottle. The heart is flabby and its pulsations are sluggish and diminished in amplitude. This is evident on fluoroscopy and can be recorded objectively in the roentgenkymogram, as in the case presented. The electrocardiogram is characterized by low voltage of all the deflections. Following the administration of thyroid the return of the basal metabolic rate to normal is paralleled by a decrease in the transverse diameter of the heart and by an increase in the amplitude of cardiac pulsations and in the voltage of the electrocardiogram. This was well illustrated in our patient by serial electrocardiograms and teleroentgenograms taken during the course of treatment.

The diminution of amplitude of the cardiac pulsations in myxedema has been attributed to a decreased power of muscle contraction. It has been shown experimentally [5] that the voluntary muscles fatigue rapidly in myxedema and that the fatigue diminishes after thyroid treatment. Apparently the same mechanism holds in the heart muscle, resulting in a decrease in pulsation, which is corrected by administration of thyroid. Formerly, it was thought that the low voltage in the electrocardiogram in myxedema was caused by the increased resistance of the myxedematous skin.[6] However, Thatcher and White [7] disproved this theory by inserting needle electrodes under the skin without producing any changes in the voltage. The latter increased only after thyroid treatment.

It is interesting to note that the increase in the cardiac silhouette, the diminished pulsations of the heart borders, the low voltage of the electrocardiogram and the very distant heart sounds are also present in pericardial effusion. Several authors therefore have attempted to explain these findings in myxedema on the basis of pericardial effusion and have educed evidence for this view. In 1927

Goldberg [8] produced hydropericardium, ascites and anasarca in sheep and goats by total thyroidectomy. More recently Gordon [9] and Freeman [10] tapped the pericardium in patients with myxedema heart and noted fluoroscopically an immediate decrease in the heart size. The same results were obtained with thyroid therapy, which prevented the re-accumulation of hydropericardium. The effusion recurred, however, when the medication was stopped. Marzullo and Franco [11] and Feasby [12] have recently reported similar cases. These observations suggest that the characteristic changes in myxedema heart may be caused by the presence of pericardial effusion. Whether the latter is the direct result of heart failure or an exudative process caused by the myxedema per se is a moot question. The absence of pericardial effusion in the ordinary cases of cardiac decompensation together with the inefficacy of digitalis in myxedema suggests that the pericardial effusion found in myxedema is not caused by heart failure, but by hypothyroidism. One should consider the possibility of myxedema heart in any patient with cardiac enlargement and serous effusions which do not respond to digitalis therapy.

Summary

A case of hypothyroidism is described in which the classical signs of myxedema heart appeared ten years after operation for hyperthyroidism. After six weeks of thyroid medication the patient's general condition improved markedly and all the cardiac abnormalities disappeared. Pericardial effusion is presented as a possible cause for the enlarged heart, the diminished pulsations and the low voltage electrocardiogram in myxedema heart.

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AURICULAR FLUTTER OF ELEVEN YEARS' DURATION WITH OBSERVATIONS ON ESOPHAGEAL ELECTRO-CARDIOGRAMS *

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AURICULAR flutter in subjects without other evidence of cardiac disease is usually paroxysmal in type. Parkinson and Bedford [1] had five cases of this nature, and Friedlander and Levine had three.[2]

Sprague and White's case [3] is unique. The patient was a 49-year-old male with auricular flutter which after five years returned spontaneously to normal sinus rhythm. Although evidence of heart disease was absent, the aorta was wide and tortuous, and suggested arteriosclerosis.

Permanent auricular flutter in otherwise normal individuals is rare. Friedlander and Levine [2] observed for four years one 64-year-old patient who fits into this category. Lewis [4] had a patient whose arrhythmia began at 50 or 53 years of age. At the age of 78 years he still had auricular flutter, but in addition showed a right bundle-branch block. Of interest was the fact that the rate of the circus which was originally 280 to 300 per minute had slowed to 210 per minute 24 years later. There were "no signs of cardiac affection other than flutter." Parkinson and Bedford [1] observed 13 cases of permanent auricular flutter but all had cardiac enlargement without definite etiology. The authors say that hypertrophy was probably due to arteriosclerosis and especially to coronary atheroma. One of this group, a 61-year-old male (case 31) with bronchitis and emphysema, was first seen in congestive heart failure in 1914. He improved with digitalis, and thereafter failure did not recur despite his refusal to continue with the drug. Auricular flutter persisted until the patient died 12 years later.

Definite evidence that auricular flutter alone can give rise to hypertrophy of the heart seems to be lacking. This is in contrast to the facts regarding auricular fibrillation which apparently can give rise both to auricular [5] and ventricular [6, 7] hypertrophy even in the absence of congestive heart failure. The present case is reported because it is an example of auricular flutter of unknown etiology giving rise in a young normal subject to hypertrophy of the heart over a period of 11 years, and finally to congestive heart failure. Standard, precordial, and esophageal electrocardiograms are discussed because of several interesting features.

CASE REPORT

W. C., a 38-year-old white truckman, was admitted to Bellevue Hospital in 1924 for serofibrinous pleuritis probably complicating pneumonia. The heart was not considered abnormal on physical examination. During 1925 the patient first experienced paroxysms of palpitation accompanied by weakness, faintness, dizziness, and dyspnea. For these complaints he was readmitted to the hospital in December 1925 and again in March 1926. Clinically the heart was not enlarged. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. A regular rhythm was interrupted by an oc-

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casional premature systole. Auricular flutter was first observed later in 1926 but was initially verified by electrocardiograms in January 1927.

There was no history of rheumatic fever, syphilis, or hypertension, and no evidence of these diseases was ever detected during the 13 years he was observed. Radial and brachial arteriosclerosis, originally absent, appeared in minimal degree before death. The basal metabolic rate was within normal limits. Tea and coffee were taken in moderation. The patient had been a heavy drinker of alcoholic beverages for many years and would often be intoxicated at clinic visits. His diet was adequate, however, in essential foods and accessory factors.

During most of the time he was comfortable, and able to carry on his work as a truckman. In 1932 he survived a fracture of the skull and of the mandible received in an automobile accident. He attended the Cardiac Clinic irregularly, and was admitted to Bellevue Hospital on eight different occasions for study. The ventricular and pulse rates were usually between 100 and 120 per minute but could be made slower with digitalis or pressure on either carotid sinus. Of interest was the fall in venous pressure that would accompany the latter procedure.[8] Dyspnea, orthopnea, palpitation, pallor, dizziness, and faintness would appear when the ventricular rate was 200 per minute, or over. Episodes of this fast rate, which were shown electrocardiographically to be due to 1 to 1 response of the ventricles to the auricles (figure 1 D), occurred at variable intervals, and usually persisted for 5 to 60 minutes. They were easily terminated by pressure on either carotid sinus, whether the patient was receiving digitalis at the time or not.[1]

The circus rhythm persisted until the patient's death in 1937 despite all efforts to restore sinus rhythm. Among the unsuccessful measures employed were full digitalization (table 1), quinidine to the point of toxicity (table 2, figure 1 E), choline chloride, acetyl-beta-methyl choline, and carotid sinus pressure.

TABLE I

Effect of Digitalis on Rate of Circus

Curve No.	Time	Mean Auricular Cycle Length in Seconds	Auricular Rate Per Minute	Ventricular Response
8442 (control)	Jan. 22, 1927	0.254	236	Irregular (1 : 2 and 1 : 3)
(4.8 gm. Digitalis given orally in period of 11 days, from Jan. 26 to Feb. 5, 1927)				
8491	Feb. 2, 1927	0.257	233	Irregular (1 : 2, 1 : 4, and 1 : 5)
8495	Feb. 5, 1927	0.258	232	Irregular (predominantly 1 : 4)

Eight teleroentgenograms were made during the 11 years of observation. Reports on the significant measurements were available in six, and are listed in table 3. In 1928 the patient weighed 150 pounds and was 65 inches tall. The predicted transverse diameter of the cardiac silhouette in a teleroentgenogram [9] for this height and weight is 12.9 cm.; at the time the actual transverse diameter was 14.0 cm. or + 8.5 per cent. The progressive increase in this diameter after 1934 is clear from the table. During the entire period of observation the patient's weight did not fluctuate appreciably. The largest transverse diameter, 16.8 cm., was obtained in 1937, when he was convalescing from congestive heart failure. The aorta became progressively wider, longer, and more tortuous. In 1934 a large left auricle was seen fluoroscopically.

TABLE II

Effect of Quinidine on Auricular Flutter

Curve No.	Time	Quinidine in Grams	Auricular Rate Per Minute	Ventricular Response
8521 (control)	Feb. 11, 1927		238	Irregular
	Feb. 23, 1927			
	9:30 a.m.	0.4		
	10:30 a.m.		206	Regular (1 : 2)
8562	11:30 a.m.	0.4		
	1:30 p.m.	0.4		
	3:30 p.m.	0.4		
	5:30 p.m.	0.4		
	Feb. 24, 1927			
8568	9:35 a.m.		186	Regular (1 : 2)
8569	3:00 p.m.		200	Regular (1 : 2)
	Feb. 26, 1927			
8573	9:30 a.m.		242	Irregular

Signs of congestive heart failure first appeared in February 1937. Satisfactory response was obtained to rest in bed and digitalis. When the patient was discharged from the hospital for the eighth and last time on July 13, 1937, all objective evidence of cardiac insufficiency had disappeared. Two days later he died at home. The mode or cause of death could not be ascertained. He was 50 years old.

Electrocardiograms

From January 1927 to July 1937 a total of 35 routine standard electrocardiograms was recorded. Additional curves were taken during special procedures. None was obtained during 1932 or during 1935.

When the patient was receiving no medication the auricular rate varied between 232 and 260 beats per minute. The ventricular response was usually 1 to 2 but on occasion was 1 to 1. The most rapid ventricular rate observed under these circumstances was 250 beats per minute (figure 1 D). It was never slower than 110 per minute. The QRS interval was between 0.08 and 0.10 sec., except in 1937 when it was 0.11 sec. (figure 1 G). There was no abnormal deviation of the electrical axis.

For long intervals the patient received 0.6 gm. of digitalis daily. During these intervals the rate of the circus varied from 232 to 275 cycles per minute though the latter rate was observed only once. The ventricular response was most often irregular and occasionally as infrequent as 45 times per minute. Table 1 shows the characteristic changes after digitalis given in daily oral doses of 0.4 gm. The rate of the circus was unchanged but auriculoventricular conduction was greatly decreased.[10]

The effect of quinidine on one of the several occasions it was given is summarized in table 2. The circus slowed to 186 cycles per minute. Once while receiving quinidine the patient developed a 1 to 1 ventricular response. The ventricular complexes were markedly aberrant, measured 0.13 sec. in width (figure 1 E), and occurred 200 times per minute. The intraventricular block was attributed to the quinidine. A somewhat similar response of auricular flutter to quinidine has been reported.[11]

Potential variations of the extremities and of the precordium[12] were recorded on November 19, 1934 (figure 2). The galvanometer connections were so made

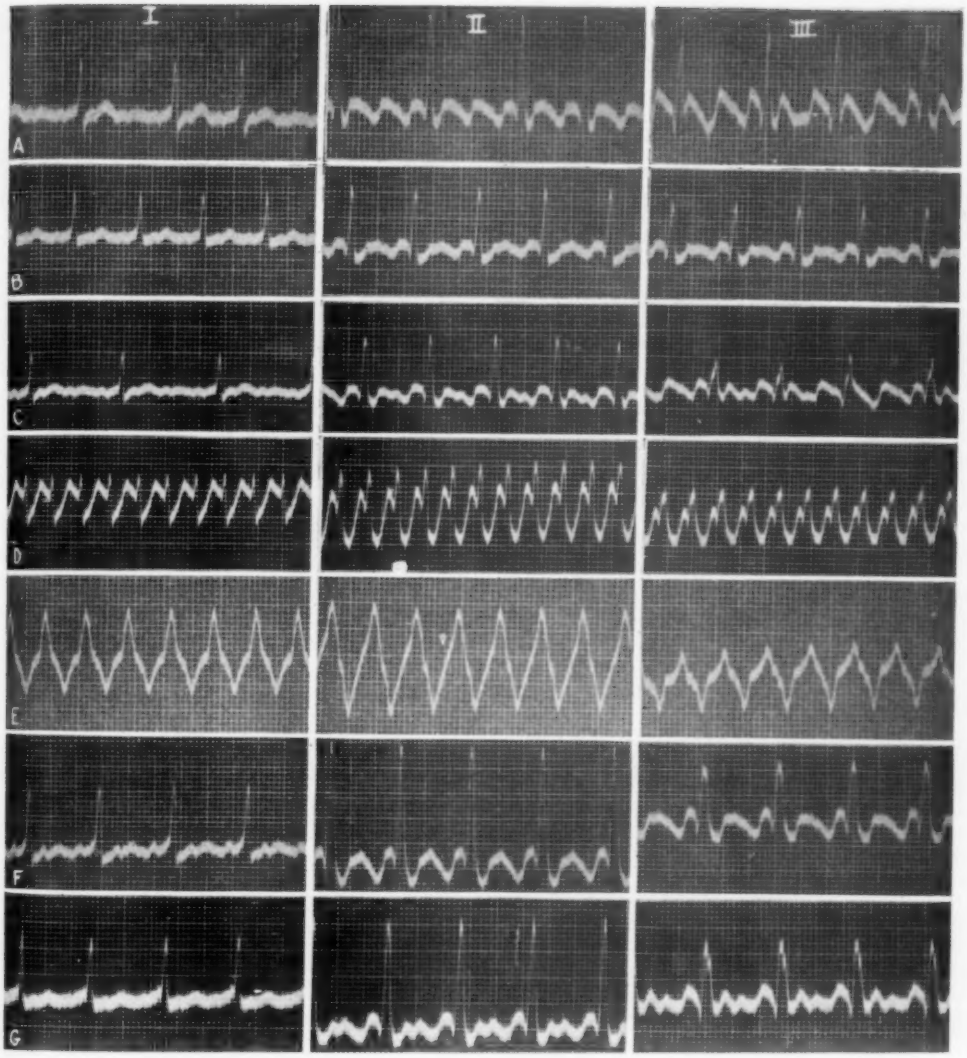

FIG. 1. Standard electrocardiograms recorded on the following dates: A, 11/14/27; B, 3/16/28; C, 5/12/29; D, 1/26/31; E, 2/13/31; F, 4/28/33; G, 7/7/37. The patient was receiving no medication when A and D were recorded. The latter shows a 1 to 1 ventricular response at a rate of 250 per minute. Curve E also shows a 1 to 1 rhythm but the rate is 200 per minute, and the QRS complexes are aberrant. The patient was receiving quinidine. The remaining electrocardiograms, B, C, F, and G, were recorded while the patient was taking 0.3 gm. to 0.6 gm. of digitalis daily for long intervals.

that a summit in the record represented negativity of the exploring electrode. The exploring electrode was circular and 1.5 cm. in diameter. The curves obtained were not abnormal in any respects.[13] The flutter waves were largest in the special leads from the right arm (V_R), the left leg (V_L), the right sternal edge (V_1), and the tip of the ensiform (V_E), but they were not more prominent in these leads than in the standard electrocardiograms.

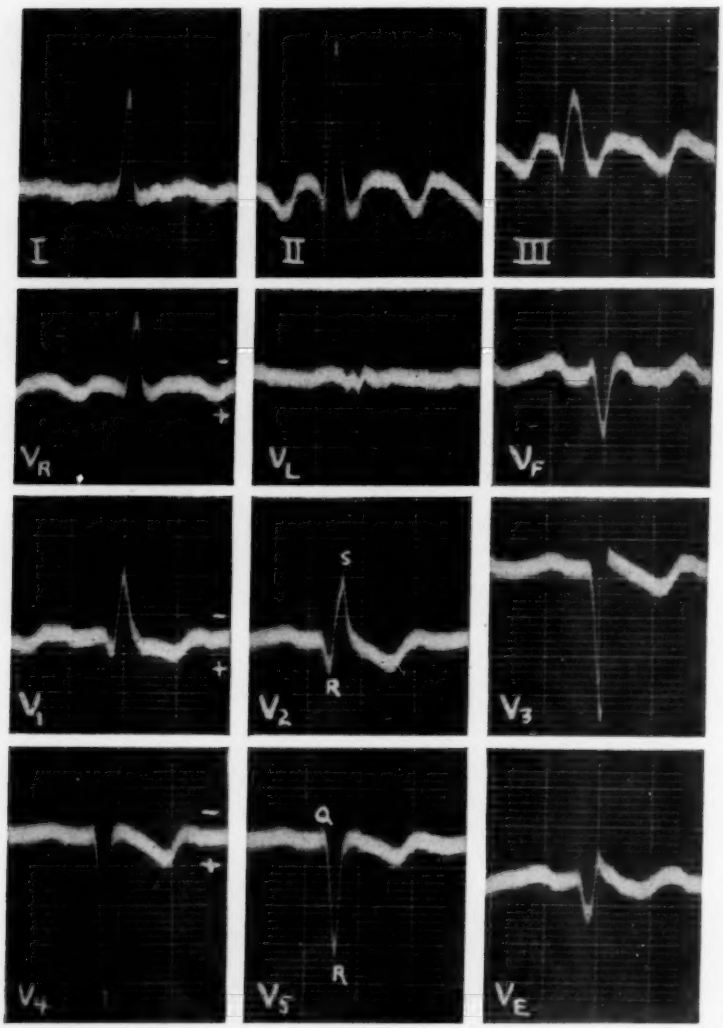

FIG. 2. Standard leads (I, II, III) and the potential variations of the right arm (V_R), of the left arm (V_L), and of the left leg (V_L) recorded at normal string sensitivity on November 19, 1934. The last six tracings were recorded at half normal (1 cm. = 2 mv.) sensitivity, and represent the potential variations of the following precordial points: V_1, fifth rib, right sternal edge; V_2, fifth rib, left sternal edge; V_3, fifth intercostal space, left parasternal line; V_4, fifth intercostal space, left midclavicular line; V_5, sixth rib, anterior axillary line; V_E, tip of ensiform. For the special leads a downward deflection represents positivity of the exploring electrode. Therefore, all deflections are labeled as though they were upside down. Time lines occur every 0.2 sec. The patient was receiving no medication.

Esophageal electrocardiograms were recorded on November 19 (figure 3) and again on December 1, 1934 (figure 4). The latter were taken simultaneously with Lead II. The esophageal electrode was a German silver cylinder 2 cm. in length and 0.9 cm. in diameter. It was connected through the galvanometer to a zero potential electrode.[12] Curves were taken with the esophageal electrode at various distances from the incisor teeth. Those obtained when this distance was 32.5 cm., 37.5 cm., 38.0 cm., and 40.0 cm. are shown in figures 3 and 4.

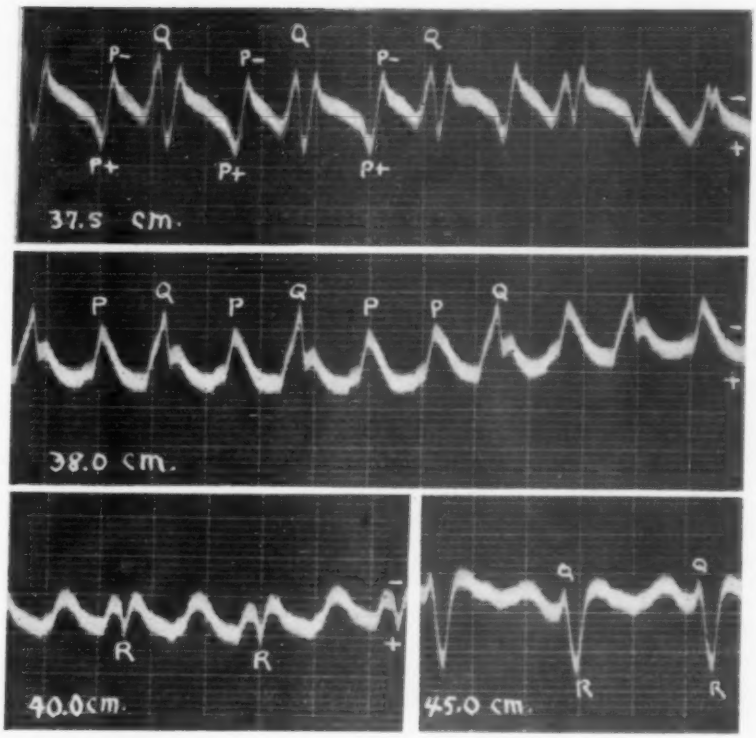

FIG. 3. Esophageal potentials on November 19, 1934, at levels 37.5 cm., 38.0 cm., 40.0 cm., and 45.0 cm. from the incisor teeth. The sensitivity of the string is half normal. A downward movement of the string shadow represents positivity of the exploring electrode. Time lines occur every 0.2 sec. Patient was receiving no medication.

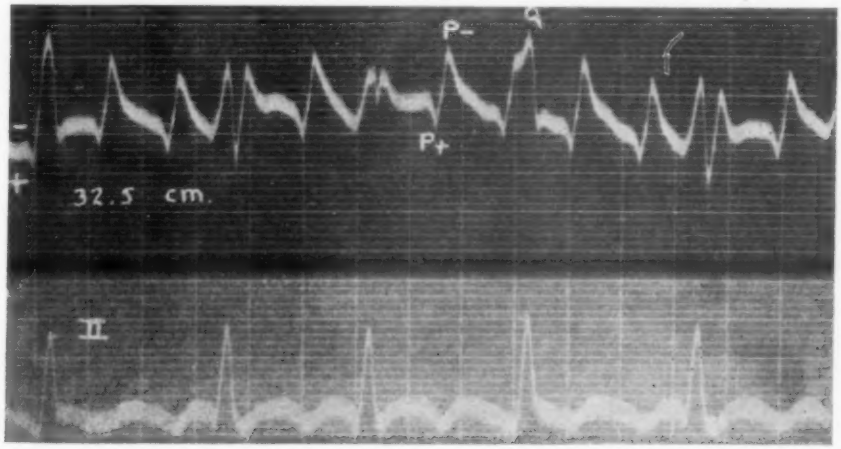

FIG. 4. Potential variations of esophagus (upper curve) 32.5 cm. from incisor teeth recorded at half normal sensitivity on December 1, 1934. Standard Lead II at three-fifths normal sensitivity is the lower simultaneous tracing. Time lines, galvanometer connections, and medication, as for previous two figures.

At levels 32.5 cm. (figure 4) and 37.5 cm. (figure 3) from the incisor teeth the electrode was in proximity to the left auricle as determined fluoroscopically. The P-wave in electrocardiograms obtained at these levels showed an initial, slow, positive deflection (P + in figures) followed by a rapid swing to a negative peak (P —). This descended rapidly at first, more slowly afterward. The positive phase is analogous to the "extrinsic"[14] or pre-intrinsic plus deflection[15] of direct or semidirect leads. The rapid change from positive to negative is similar to the "intrinsic" deflection[14] of direct leads or the intrinsicoid deflection[16] of semidirect leads. The gradually declining negative phase is probably caused by doublets of recovery in the auricle.[17, 18] This phase is of some clinical importance since it does not appear in the esophageal electrocardiograms of patients with ectopic auricular tachycardia.[19, Part II]

It will be noted that the P-wave lost its diphasic character when the electrode was 38.0 cm. from the incisor teeth but the ventricular complex still consisted of a single slurred negative deflection as in leads from higher levels. It is labeled Q for the sake of consistency with the nomenclature now used for precordial electrocardiograms.[20] At the levels under consideration the ventricular complex is negative, probably because the esophageal electrode is opposite the auriculoventricular orifice at the base of the left ventricle. It is, therefore, a semidirect lead from the cavity of the left ventricle which has been shown by Wilson and his associates[21] to be negative during the greater part of ventricular excitation. The usually negative potential of the right

TABLE III

Cardiac Measurements in Cm. of Six Teleroentgenograms Recorded on the Dates Indicated

Date	Transverse Diameter	Width of Aorta	Width of Pulmonic Fields
11/15/28	14	5.2	27.4
5/21/29	13.7	6.1	—
4/20/34	13.9	6.7	26.6
11/15/34	15.2	7.2	28.0
3/27/36	15.9	7.3	28.0
2/26/37	16.8	6.5	27.5

arm in normal subjects has been attributed to the relationship of this extremity to the base of the heart.[13] The similarity between the potential of the right arm (V_R, figure 2) and the esophageal ventricular complexes recorded between 32.5 cm. and 38.0 cm. from the incisor teeth (figures 3 and 4) is to be noted. It is true that the Q-wave of these higher esophageal potentials is simultaneous with the R-wave of Lead II (figure 4), but it is created in a different way. The evidence that this is true is present in esophageal leads taken at 40.0 cm. and 45.0 cm. from the incisor teeth (figure 3). In these leads the QRS complex is principally a positive deflection, R, preceded in the lead from the lower level by a negative wave or Q. This R is also approximately simultaneous with R of Lead II. This is due to the fact that the esophageal electrode is at these lower levels juxtaventricular and principally on the positive side of the same wave of excitation responsible in large part for the R-wave in Lead II and for the Q-wave in leads from higher levels in the esophagus.

In a semidirect lead from the apex of the heart a ventricular complex similar to that obtained at 45.0 cm. from the incisor teeth in the esophagus should be obtained, assuming that the heart muscle displays equal electrical activity in all portions. This is true in the present situation, for Leads V_4 and V_5 (figure 2) are strikingly similar in form to the lowest esophageal lead (figure 3, 45.0 cm.).

Evidence that excitation in auricular flutter travels upward in the posterior part of the left auricle was obtained in two ways. First, as the electrode was lowered in the esophagus the initial positive phase (P +) of auricular excitation disappeared

(figure 3, 38.0 cm.) and only the negative portion remained. In a sinus rhythm the reverse is true, an entirely positive deflection being obtained from leads more than 40 cm. from the incisor teeth.[22] This would indicate that in the case under discussion excitation was proceeding in the main away from the esophageal electrode when the latter was at or below the auriculoventricular junction. Second, the time of the auricular intrinsic deflection in esophageal leads at 32.5 cm., 35.0 cm., and 37.5 cm. from the incisor teeth was measured with respect to a fixed auricular wave in Lead II. The values obtained respectively were 0.078 sec., 0.094 sec., and 0.102 sec. This means that excitation reached the lowest explored portion of the left auricle 0.024 sec. earlier than the highest explored portion. If it is assumed that the esophageal electrode was in or very close to the path of the mother wave of the circus the rate of conduction is calculated at 2083 mm. per sec. W. Hurst Brown[19] observed a case of flutter in which excitation took 0.0230 sec. to travel between two points 38 cm. and 34 cm. from the incisor teeth respectively. On the basis of his figures, making assumptions as above, the rate of conduction over this strip of 4 cm. was 1739 mm. per sec.

Comment

Why this patient had auricular flutter remains unanswered. Neither from the history nor from the later structural changes in the heart could the cause be determined. The flutter antedated the appearance of arteriosclerosis. The only possible etiological factor was the excessive use of alcohol, a drug which can inaugurate various cardiac arrhythmias. That alcohol can produce permanent auricular flutter in the absence of organic heart disease is unlikely.

The progressive increase in the size of the heart in the absence of the usually accepted causes of myocardial hypertrophy, and before the onset of congestive heart failure, makes it probable that the abnormal rhythm of the auricles, and the rapid and variable ventricular rate were alone responsible for the anatomical changes observed.

Summary

Auricular flutter of 11 years' duration and of unknown etiology in an otherwise normal individual is reported. Progressive cardiac hypertrophy could be attributed to no cause other than the circus rhythm. Standard and precordial electrocardiograms were not beyond normal limits. Intraventricular block was observed as a toxic manifestation of quinidine therapy on one occasion when the ventricular response to the auricles was 1 to 1. Esophageal electrocardiograms showed that excitation reached the lowest portions of the left auricle earlier than the upper portions. With respect to the ventricular deflections the similarity of an apical lead to a juxtaventricular esophageal lead, and of the potential variations of the right arm to the juxta-auricular esophageal potentials is demonstrated.

The authors express their sincere thanks to the members of the Third Medical Division and Cardiac Clinic of Bellevue Hospital who so diligently collected data and made observations on this case for more than a decade.

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MYASTHENIA GRAVIS; A DISCUSSION, WITH PRESENTATION OF A CASE ASSOCIATED WITH A THYMOMA *

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MYASTHENIA gravis, a symptom-complex manifested by an incapacity of one or more groups of voluntary muscles for sustained effort, is without any demonstrable involvement of the nervous system.

Thomas Willis is credited by several authors [1, 2] with having first described the disease; but Wechsler [3] claims that Wilkes in 1877 deserves that credit. Erb [1] gave a clear and classical description in 1878 but believed that the condition was due to pathological changes in the central nervous system. Oppenheim [4] claimed credit for first clearly differentiating the disease in 1887 and named it bulbar paralysis without pathological lesions. Jolly,[2] in 1895, demonstrated, by electrical stimulation, rapid fatigue reactions and named the disease myasthenia gravis pseudoparalytica. The disease has also been called Erb-Goldflam disease and asthenic bulbar paralysis. Buzzard,[5] 1905, described a lymphocytic infiltration in skeletal muscles and this distinctive lymphorrhagia was reëmphasized by Norris,[6] and others.

Oppenheim,[4] in his description of the disease, made the statement: "I think it not impossible that in the future the disease may in some cases be cured by the removal of a tumor which is the source of toxic products. Tumors have already been successfully removed from the anterior mediastinum." Weigert,[6] 1901, was the first to report a case of myasthenia gravis associated with a tumor of the thymus gland. Following Weigert's report, this anatomic relationship has been reported with increasing frequency. Starr [7] (1912) collected 250 cases of myasthenia gravis for analysis and found enlargement of the thymus in 28 per cent. In 1917, Bell [8] collected 56 autopsied cases of myasthenia gravis reported after 1901 and found that enlargement of the thymus had been noted in 17 and a tumor in another 10, so that some lesion of the thymus had been found present in almost 50 per cent. Keschner and Strauss [9] quote Greenfield as pointing out "that negative observations in regard to the thymus are of little value unless the mediastinum has been searched carefully and systematically, since thymus tissue can be readily overlooked in the fat of this region."

In 1936, Norris [6] added to Bell's series 10 cases, in seven of which thymic lesions were recognized. He stated: "I am of the opinion that pathologic changes may be found in the thymus in cases of myasthenia gravis in direct ratio to the care with which they are sought." Alter and Osnato [10] also state that "all cases of myasthenia gravis with definite pathologic observations should be recorded, not only for the reason of their rarity, but that they may serve toward the construction of an explanation of the pathology of the disease, confirm part of it or offer useful hints for future observations." One year after his first report, Norris [11] added two more cases to bring his series to 82 cases of myasthenia that came to autopsy. Peer and Farinacci [12] added one case and Miller,[13] in February of this year, added five more autopsied cases, of which four had thymic lesions. To this group, I wish to add one case, bringing the total of

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autopsied cases of myasthenia gravis since 1901 to 89, in *43 (48 per cent) of which a lesion of the thymus gland was the outstanding feature.*

Miller [13] quotes Lievre as concluding that:

"1. Tumors of the thymus are frequently found in myasthenic patients.
2. Microscopic tumors may easily be missed at autopsy.
3. There is a definite causal relationship between the thymus and myasthenia gravis and roentgen investigation followed by irradiation or surgical removal is the procedure of choice."

A clearly defined classification of thymic tumors has never been made. Margolis [14] feels that not only because of the double origin of the thymus but also because of the polymorphism of the cells found, a rigid classification is impossible and that the designation of thymoma for all thymic tumors is the only solution at present. Symmers [15] classifies tumors of the thymic region as peritheliomata, lymphosarcomata, epitheliomata, and spindle-cell sarcoma and has found not only simple hyperplasia of the thymus but also malignant tumors in cases of myasthenia gravis. Ewing,[16] however, classifies tumors of the thymus in association with myasthenia gravis in a category separate from other thymic tumors. Norris [6] feels that all thymic tumors associated with myasthenia are benign thymomas or adenomas. Bell [8] found only one possible case of malignancy in his series of 27 thymic lesions associated with myasthenia gravis and over 60 cases of thymic malignancies which were not associated with the disease. Miller [13] states that Obiditsch studied a series of thymic tumors and concluded that those composed predominantly of small round cells more often were associated with symptoms of myasthenia than were epithelial and malignant types.

Spinal fluid examinations in myasthenia gravis are almost uniformly negative and central nervous system lesions are usually absent. Of various blood disturbances, Noyes [17] states that the most frequent departure from normal is polycythemia (also found in the case cited below). Hart [18] found a marked decrease in sugar tolerance in his own and several other cases (also found in the case cited below). Reports concerning metabolic changes such as increase or decrease of creatine and creatinine excretion are so variable as to lead one to conclude that these changes are independent of the disease itself.

Myasthenia gravis attacks both sexes with about equal frequency. It usually appears between the ages of 20–50 years, although Rothbart [19] cites cases in the same family in which the onset was at the ages of six weeks, three months, and two years. Others have reported the onset at the age of 70 years. The remissions and exacerbations are so characteristically part of the disease as to be included with the symptoms. Headaches, various paresthesias and pains, stiffness of the muscles, and generalized weakness may precede the disease by several months.

The onset is usually insidious although acute infections and pregnancy have sometimes caused abrupt onset of symptoms and Hyland [20] has observed that repeated minor infections, emotional stress, hot baths and mild gastrointestinal upsets are apt to cause marked exacerbation of symptoms. Starr [7] observed in a series of 315 cases that weakness of arms and legs preceded by days to months bulbar symptoms in 38 per cent. Usually, the first noticeable complaint is a diplopia due to weakness of the extrinsic muscles of the eyes or a ptosis due

to weakness of the levator palpebrae superioris. Involvement of the muscles of mastication is of frequent occurrence, as is dysphagia, nasal regurgitation of fluids, dysarthria or aphonia, absence of pharyngeal reflexes and paroxysmal dyspnea. Many of the patients complain of an annoying, stringy mucus. The symptoms are milder in the morning and increase in severity during the late afternoon and evening.

The diagnosis is usually quite easy. The symptoms, the muscular reaction to electricity, the myasthenic reaction to light, absence of muscular atrophy and reaction of degeneration, absence of characteristic changes in deep reflexes, the presence of lymphorrhages in biopsied muscle, roentgenogram finding of a mediastinal tumor, and the prostigmin test all aid in establishing the diagnosis. The Jolly reaction is one where a tetanizing faradic current applied to the muscle of a myasthenic patient repeated at intervals of seconds will cause a very rapid diminution and finally loss of all muscular response followed by recovery after a short rest. The pupils of the eyes show a similar loss of power to rapid stimulation by light. Crosby [21] states that " A circular, sharply defined, flattened, non-pulsating mass in the anterior wall of the thorax, in the absence of other evidence to the contrary, justifies a tentative diagnosis of probable thymoma." Doub [22] gives a good differential diagnosis of the roentgen-ray characteristics of thymus neoplasms from those of other chest tumors. He also describes a technic for deep irradiation treatment. The use of prostigmin as a diagnostic test was first reported by Viets and Schwab,[23] who administered 3 c.c. of injectable prostigmin and gr. 1/100 of atropine. This work was confirmed by other observers.[24, 25, 26] Keschner and Strauss [9] give an excellent differential diagnosis of myasthenia gravis from various neurological disorders.

The course of the disease is usually progressively downhill despite the use of such drugs as prostigmin. Many cases die within the first year, often of sudden suffocation. However, spontaneous remissions are reported and Laurent [27] cites a case of myasthenia gravis with undoubted symptoms for 29 years.

The accepted regime, until recently, was absolute bed rest, abstinence from massage and electrical stimulation, and the use of tonics and glandular extracts. In 1921, D'Amato [28] reported marked improvement in a case of myasthenia gravis from the use of epinephrine. In 1930, a short report by Dr. Harriet Edgeworth [29] gave new impetus to the treatment. Herself a victim of the disease, Dr. Edgeworth found ephedrine abated the symptoms markedly. Boothby [30, 31] and others described the use of glycine, advocating five grams of glycine six times daily. Using 10 to 20 mg. per kilo of body weight, Minot and his associates [32] treated five cases with guanadine hydrochloride dissolved in normal saline and administered intravenously, obtaining good results in all. Viets and Schwab,[2] however, were unable to confirm these results.

In 1934, noting the resemblance of myasthenia gravis to curare-poisoning, Walker [33] used physostigmin because of its action as a partial antagonist to curare. Denny-Brown [34] suggested the use of physostigmin salicylate orally with belladonna to prolong the good effects and minimize its toxicity. In December 1934, because it was less toxic, Mary Walker began to use prostigmin, demonstrating the results on two cases before the Royal Society of Medicine and reporting her results in February 1935.[35] Her results were quickly confirmed by Pritchard,[36] Laurent [37] and others. Everts [38] was the first to report on the oral use of prostigmin, finding it more successful than the injectable variety because of its longer effect and lessened toxicity. He also found that large doses

of potassium chloride augmented the general improvement of the patient, thus confirming the work of Laurent and Walther.[39] Kennedy and Wolf,[26] however, found that some cases became refractory to prostigmin within 1 to 4 months and Harvey and Whitehill [25] cited three cases where the early beneficial results decreased with each succeeding injection of prostigmin. Hyland [20] states that the transient relief is followed by increased weakness and Minski and Stokes [40] point out that the value of prostigmin is reduced by its toxic manifestations and the difficulty of control in ambulatory cases. Simon [41] found that 1 c.c. of anterior pituitary extract given subcutaneously daily gave excellent results in two cases but other observers have been unable to confirm this work.

Hsü and Ch'Eng [42] state that in 1913, Schumacher and Roth reported favorable results in the disease by extirpation of the thymus and that Pierchalla in 1921 advocated irradiation of the thymus as a therapeutic test even when no thymic enlargement could be demonstrated by roentgen-ray. Halsted [43] stated that when roentgen-ray therapy to the thymus gland was used in cases of Graves' disease that did not get relief from thyroidectomy, prompt and striking improvement was obtained, and stated further that " asthenia, which was common to all the cases, has been particularly influenced." It is my belief that the asthenic symptoms in these cases were myasthenic manifestations and the relationship between thyrotoxicosis and myasthenia gravis should be further investigated.

Mella [44] reported complete recovery followed deep roentgen-ray over the thymus gland in a patient with myasthenia gravis. Keschner and Strauss [9] had two cases that were subjected to roentgen-ray therapy with resulting disappearance of the thymic shadow and a complete disappearance of symptoms. Decker [45] mentions three cases which were treated by thymectomy with good results. Hyland,[20] using roentgen-ray therapy of the thymus in four cases, obtained marked improvement in two within a short time; slow but continuous improvement in the third six weeks after the last treatment; and partial relief six months after the last treatment in the fourth case (who had had a three year progressive history until that time). Ayer [46] states that he had one cure due to roentgen-ray therapy of the thymus but gives no details. Riven and Mason [47] report a case of myasthenia gravis with enlargement of the thymus that had several remissions after repeated courses of deep roentgen-ray therapy. Thorner and Yaskin [48] treated three patients without any change from the pretherapeutic state but the amount of therapy was small and the length of observation following treatment was evidently short. Miller [13] recommends irradiation and surgical removal of the thymus in cases of myasthenia gravis.

Case Report

Mrs. A. M. W., a white woman, 56 years of age, began to note slight fatigue and malaise in 1938. One year later, she noticed first a twitching, then a drooping of the right eyelid with a transient double vision followed in three months by slurring speech with a nasal tone. A decreased sugar tolerance led to a diagnosis of diabetes mellitus and a dietary régime was instituted. However, the symptoms progressed rapidly and one week later there occurred a drooping of the jaw, a difficulty in chewing and swallowing, and nasal regurgitation of fluids. She also began to experience attacks of dyspnea. These symptoms with drooling of saliva were present upon the admission of the patient to the Johns Hopkins Hospital in December 1939. A diagnosis of myasthenia gravis was made and through the courtesy of Dr. F. R. Ford, the following data are recorded:

Blood Analysis	
Red blood cells:	5,420,000
Hemoglobin:	110% (16 gm.)
White blood cells:	7,750
Non-protein nitrogen:	30 mg. per cent
Calcium:	10.4 mg. per cent
Cholesterol:	177 mg. per cent
Basal metabolic rate:	plus 12 (satisfactory test)
Wassermann test:	four plus
Roentgen-ray:	Skull—skull and sella normal Chest—negative

Glucose Tolerance Test	
Fasting	129 mg. per cent
9:30	230 " " "
10:00	287 " " "
11:05	267 " " "
12:05	180 " " "

Guanidine, glycine and ephedrine were all tried but found to be ineffective. Prostigmin did help the patient but was not as successful as in most cases. Small doses of insulin were without any result.

In February 1940, the patient was first seen by me, at which time despite ephedrine gr. 3/8 t.i.d., and 105 mg. of oral prostigmin augmented by hypodermic injections of that drug, she was able to take only liquid or puréed foods by painful and slowly swallowed teaspoon doses. She could speak only one or two words at a time, had to continuously hold up her jaw with her hand, complained of an annoying tenacious mucus in her throat and of progressive weakness. The pharyngeal reflex was abolished. Because of the rapid progression of symptoms, the patient was hospitalized on February 20, 1940 at the Swedish Hospital for roentgen-ray therapy. It was planned to administer a total dose of 3000 r over the anterior mediastinum in ten days. Four hours after admission, she received 300 r (200 KV, 2 Cu plus 1 Al, 10 × 10 cm. portal, 23 r/minute). The following morning she stated that she felt stronger and, for the first time since the onset, her jaw stayed closed without manual support. However, that afternoon she died suddenly of what appeared to be an acute cardiorespiratory failure. The similarity of this sudden collapse without any cyanosis to that of sudden thymus deaths in babies is most striking. Whether this sudden death 20 hours after the first roentgen-ray treatment is a coincidence or a result is a matter of conjecture.

At the autopsy performed by Dr. D. H. Nickson, the only significant anatomic finding was a retrosternal, encapsulated, somewhat nodular tumor mass (figure 1) adherent to, but easily stripped from, the anterior, upper margin of the pericardium. This mass measured 5.3 by 3 by 1.8 cm. and weighed 16.6 grams (Gudernatsch [49]

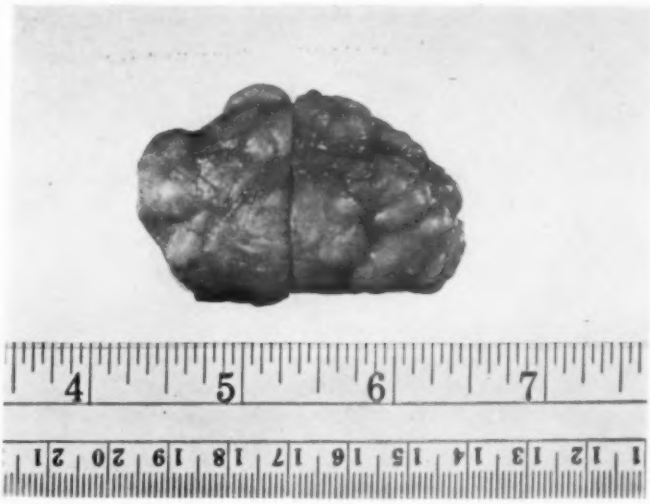

FIG. 1. Gross specimen.

quotes Hammar as stating that the thymic parenchyma weighs 1.48 grams at 45 to 55 years of age). On the cut section, it was found to be a soft, uniformly gray tumor, somewhat lobulated. Microscopic sections (figure 2) revealed fields of small, round lymphoid cells and others where large, pale epithelial cells with clearly defined nuclei and indefinite polyhedral cell borders predominated. Less than 5 per cent of the cells showed mitotic figures. Scattered throughout were Hassal's bodies. There was a well-defined capsule with trabeculae dividing the gland into lobules but no definite cortex and medulla could be defined.

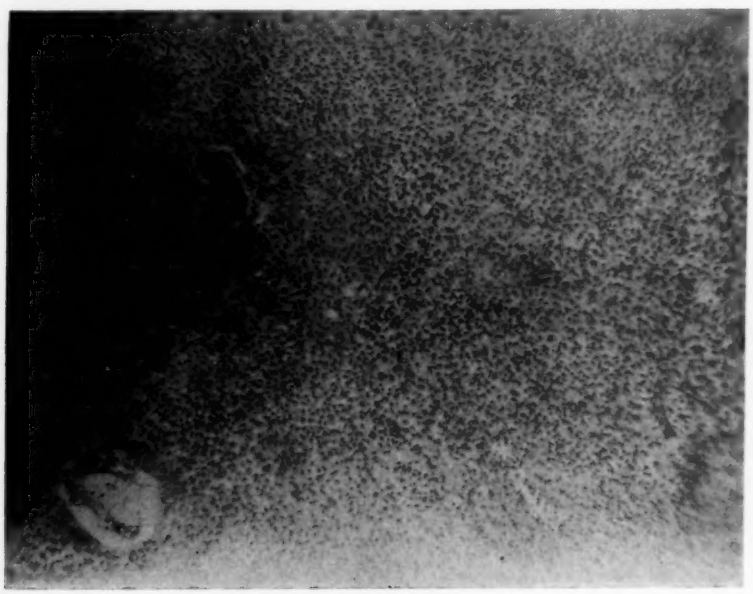

FIG. 2. Photomicrograph 200 ×.

FIG. 3.

Summary

1. A case of myasthenia gravis associated with a thymic tumor is presented.
2. The etiology and the therapy of myasthenia gravis are briefly reviewed.
3. The pathology of myasthenia gravis is discussed with particular reference to tumors of the thymus gland.
4. The literature is reviewed with reference to the treatment of myasthenia gravis by extirpation of or by deep roentgen-ray therapy to the thymus.

Conclusions

1. A negative chest film does not mean the absence of thymic enlargement.
2. Complete roentgenological examination of the chest should be made in all cases of myasthenia gravis, as thymic tumors may be obscured by the heart shadow in the anterior-posterior views.
3. Where a definite thymic tumor is found by roentgen-ray, extirpation of the gland should be considered.
4. Deep roentgen-ray therapy should be carried out in all cases of myasthenia gravis even where there are negative chest plates.
5. Several consecutive roentgen treatments may be necessary and such a course may have to be repeated one or more times before a remission or cure is effected.

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EDITORIAL

IMMUNITY TO MALARIA

THAT human beings can acquire a considerable degree of resistance to malarial infection has been known for many years. It is a matter of common observation that native inhabitants of tropical regions in which malaria is continuously prevalent—the "hyperendemic" areas—acquire a resistance or at least a tolerance for the infection, so that they show no clinical symptoms of malaria although susceptible newcomers quickly become ill and often succumb to the disease. The conditions under which such immunity develops have been studied with particular care by British observers such as Thomson, Christophers, and James.[1] These studies have shown that practically everyone in the community becomes infected in early childhood and is continuously exposed to reinfection. In one such community Wilson[2] estimated from the prevalence of infected *Anopheles* mosquitoes in the houses that on the average each inmate would receive an infective bite once in twelve days.

The children under two years of age are clinically ill with fever and show enlargement of the spleen and large numbers of parasites in the blood—a condition termed by Christophers the stage of acute infestation. In spite of this these children may show surprisingly little impairment of health if the malaria is not complicated by dietary deficiencies or other forms of parasitism. Possibly some degree of racial immunity may have developed as a result of natural selection during many generations of exposure. In older children parasites are still present but in smaller numbers, and febrile attacks occur only once in two to four weeks—the stage of immune infestation. In adults there may be one or two mild febrile attacks a year, with otherwise no manifestations of illness. Parasites in small numbers can be found in the blood in from 25 to 50 per cent of the cases.

The resistance so acquired is restricted to the species of malaria concerned and largely to the local strains of that species. If such an individual moves into a different region, he may acquire acute malaria from other strains present there. The period of about 15 years elapsing before a newcomer into an infested district secures maximum protection is believed to be the time required for him to acquire and develop an immunity to all the strains of each species occurring in the district.

This resistance is maintained largely by continuous exposure to reinfection. If a native moves into a region free from malaria, he gradually loses his resistance, and on returning to his former home is likely to become

[1] For an excellent review of much of this work see: ASHFORD, M.: The nature of immunity to malaria in its relationship to antimalarial therapy, Am. Jr. Trop. Med., 1936, xvi, 665–678.

[2] WILSON, D. B.: Implications of malarial endemicity in East Africa, Trans. Roy. Soc. Trop. Med. and Hyg., 1938–39, xxxii, 435–446.

acutely ill with the disease. If the frequency of reinfection in such a community is reduced (but not eliminated) by attempts to eradicate mosquitoes, for example, so that the development of active immunity is retarded, there may be an actual increase in the amount of clinical malaria observed. Some therefore question the advisability of undertaking measures of this sort where conditions are such that they can be only partially successful.

This resistance develops fully only if the disease is allowed to run its course without treatment. Quinine or other antimalarial drugs delay and tend to reduce the degree of immunity attained. Furthermore the full effectiveness of quinine depends upon the development of some degree of active immunity by the individual as a response to the infection. The drug temporarily suppresses the clinical manifestations of malaria but by itself does not eradicate the infection. The indiscriminate administration of quinine in such communities in which frequent reinfection can not be prevented may be actually harmful, many believe, by interfering with the development and maintenance of an effective active immunity. Treatment should be restricted, perhaps, to those acutely ill as a symptomatic measure, and not given merely in a vain hope of eradicating the infection.

Experimental work with malaria in birds and monkeys and also in man has, in general, confirmed and amplified the conclusions based on these clinical observations. In the case of avian malaria, it was shown by Wasielewski (1902) that birds which survived the acute attack continued to have a latent infection demonstrable only by the inoculation of blood into normal birds. Such birds can not be reinfected (superinfected) with the same species of parasite as long as the infection persists, although they are susceptible to infection with other species of malaria. A few such birds, however, have succeeded in eradicating the infection completely, and they were then susceptible to reinfection.[3]

Monkeys also develop a similar type of latent infection during which they resist superinfection with the same strain of parasites.[4] They show no increase in resistance to other species of malaria, and are usually susceptible to infection with exotic strains of the same species.

The therapeutic use of malaria in the treatment of syphilis has made possible extensive experiments on man. Particularly careful observations have been made by James [5] in England, and by Boyd [6] and his associates in this country. In the case of both benign tertian and estivo-autumnal malaria, if the disease is allowed to run its course without treatment, the individual becomes resistant to reinoculation with the same strain of parasite. This

[3] MANWELL, R. D.: Reciprocal immunity in the avain malarias, Am. Jr. Hyg., 1938, xxvii, 196–211.

[4] MULLIGAN, H. W., and SINTON, J. A.: Studies in immunity in malaria. Superinfection with various strains of monkey malarial parasites, Rec. Malaria Survey India, 1933, iii, 529.

[5] JAMES, S. P.: Some general results of study of induced malaria in England, Trans. Roy. Soc. Trop. Med. and Hyg., 1931, xxiv, 477–538.

[6] BOYD, M. F.: On strains or races of the malarial parasites, Am. Jr. Trop. Med., 1940, xx, 69–80.

resistance, however, does not extend to other species or to different strains of the same species. The immunity lasts for at least three years. It is still uncertain whether or not the immunity in man depends upon the persistence of some parasites in the body (premunition). It does, however, last long after parasites can no longer be demonstrated by inoculations of 10 c.c. of blood.

Immunity in malaria thus manifests itself in two ways: by a marked diminution in the number of parasites in the blood; and by the ability of the individual, although infected, to live free from sickness under conditions which would cause intense and practically continuous illness in the ordinary individual. There is still considerable doubt, however, as to the mechanism by which this resistance is brought about. The earlier attempts to demonstrate specific antibodies in the serum were for the most part unsuccessful, although Kingsbury (1927) reported obtaining positive complement fixation tests. It was thought that immunity depended mainly upon changes in the tissues, and hyperplasia of reticuloendothelial cells was demonstrated, particularly in the spleen. Furthermore, splenectomy in birds and monkeys in many cases markedly reduces their resistance to malaria and may precipitate an acute fatal attack in an animal harboring a latent infection. It is difficult, however, to explain the remarkable degree of species and strain specificity of the immunity solely on the basis of changes in the tissue cells.

More recently Coggeshall, Eaton and their associates [7] have demonstrated conclusively the presence of antibodies in the blood of monkeys and human beings with chronic malaria. Their success was largely owing to the use of a more satisfactory antigen prepared from the blood of monkeys heavily infected with *Plasmodium knowlesi,* in which 50 per cent or more of the cells contained parasites. Agglutination, complement fixation and some degree of protective power were demonstrated. Agglutination and protective power were apparently restricted to this species, but complement fixation was less specific in that positive reactions were also obtained with sera from human cases of benign tertian and estivo-autumnal malaria.

It is not likely that these reactions will attain much value as diagnostic procedures. The titer was usually low, the preparation of the antigen difficult and the technic relatively tedious and complicated. The work is interesting, however, in showing that the mechanism of immunity to this protozoan parasite is probably not fundamentally different from that in ordinary bacterial infections.

P. W. C.

[7] Eaton, M. D., and Coggeshall, L. T.: Complement fixation in human malaria with an antigen prepared from the monkey parasite, *Plasmodium knowlesi,* Jr. Exper. Med., 1939, lxix, 379–398.

REVIEWS

Manual of Cardiology. By WILLIAM DUNCAN REID, A.B., M.D., F.A.C.P. 364 pages; 22.5 × 15 cm. Oxford University Press, New York. 1940. Price, $3.50.

With a bedside type of presentation, the author furnishes in this volume a personal summary of the important and more recognized aspects of cardiac disease. The book is written chiefly from the standpoint of the student in the nature of a guide to cardiology and is not meant to replace the standard textbooks in which the subject matter and controversial issues are more scientifically treated. Rather it discusses the essentials of diagnosis and treatment of heart disorders in the simplest of terms, with the avowed purpose of aiding the student to apply the textbook material. Only accepted methods having ease of application and bedside usefulness are mentioned, but these are fully evaluated in the light of the author's personal experience.

The book is divided into three parts. Section I deals in an informal conversational manner with the diagnosis, prognosis, treatment and prevention of heart disease. Under diagnosis, the history, physical examination, special examinations and cardiac rhythms are each logically interpreted as to value, important points and means of application. An interesting feature is the use of marginal lines here and there for emphasis and mastery. At the end of the section are appended two charts, one summarizing the data just mentioned, and the other giving the essential characteristics in the differential diagnosis of the common congenital defects.

In Section II, the case histories of 56 patients from the author's files are presented briefly, each with a few questions at the end concerning important points in diagnosis and treatment. Some of the reports are purposely incomplete to stimulate the reader's thought regarding further examinations and details necessary to achieve the diagnosis.

In Section III, the questions raised in Section II are fully discussed and answered for each of the case reports, with arrangements in the same order as in the second section.

In summary, this manual reduces cardiology to its simplest terms for the undergraduate student of medicine, although it should also prove helpful to many general practitioners who feel uncertain regarding their knowledge of cardiac diseases.

R. W. G.

Specialties in Medical Practice. Edited by EDGAR VAN NUYS ALLEN, M.D. Volume I, pages 1–441; Volume II, pages 442–934; 19.5 × 26 cm. Thomas Nelson and Sons, New York. 1940. Price, $25.00.

The purpose of these volumes is to present to the general practitioner a condensed statement of those parts of each specialty which he can utilize in his practice. The venture is experimental and the final test of whether it has succeeded must be the extent to which general practitioners maintain their subscriptions. It appears to the reviewer that the various authors who have contributed have done their best to present their respective special fields in the manner most useful to the non-specialized readers. The section on ophthalmology seems particularly well done in this respect. However, one may doubt the advisability under the present conditions of practice in this country of the family physician undertaking the operation for chalazion so minutely and interestingly described by the author. In the section on neurology the author has had to contend with the difficulty of condensing too large a subject into too small a space. The result is a section which does not differ greatly from what may be found on the subject of diseases of the nervous system in any of the standard practices of medicine which the general practitioner already possesses. Indeed the discussions of meningitis

and of carbon monoxide poisoning, for example, are far less adequate than those to be found in the usual practice.

The section on orthopedic surgery is too condensed to be of great practical value except perhaps as a reminder to one already well acquainted with this field. Obstetrics and gynecology are dealt with at some length and apparently in an adequate and practical manner.

The section on endocrinology should be very valuable to any careful reader. In particular the discussion of the essentials in thyroid surgery should be of interest to those who have not paid previous attention to this matter.

In summary, these volumes are an interesting venture in popularizing the specialties, but not all specialties lend themselves equally well to this form of treatment. It is questionable whether or not the well trained younger practitioner will do better with this system or through a policy of purchasing monographs and standard texts.

M. C. P.

An Introduction to Biochemistry. By WILLIAM ROBERT FEARON. Second edition. 475 pages; 14.5 × 22 cm. The C. V. Mosby Company, St. Louis. 1940. Price, $3.75.

The author has "sought to approach the living organism . . . along the less worn path of inorganic biochemistry," since "the microessential constituents of tissues remind us of the fundamental importance of the chemical elements associated with life." Hence the first 62 pages of the book, due to this unusual approach, are devoted to a detailed description of biological elements, inorganic compounds, solutions and colloidal systems. The next 123 pages are devoted to a thorough presentation of carbohydrate, protein and lipid chemistry. This portion of the book is particularly excellent, as are the chapters on biological pigments, enzymes and nutrients (81 pages). The material on digestion and intermediary metabolism (58 pages), although brief, is adequate and contains numerous helpful and instructive diagrams. Then follow chapters on tissue respiration, purines and pyrimidines, nitrogenous bases, urea and other urinary products of excretion (87 pages). A chapter on hormones and a few words on blood and tissue fluids complete the book. An outstanding feature of this text is the ability of the author to write clearly and concisely and to outline and simplify the subject matter. Throughout one is continually impressed by the author's originality especially as to style and as to selection and presentation of material. It should prove to be a satisfactory text for students in general biochemistry.

Absent, however, is the clinical aspect which characterizes the style and subject matter of most of our popular texts on biological chemistry. The author states that he has avoided "some regions of tissue chemistry, especially blood, muscle and nerve, as it is difficult to survey them adequately without physiological and histological assistance outside the scope of this venture." Be that as it may, this reviewer feels that the students and teachers of American medical schools will insist on a text which treats biochemistry more fully from the physiological point of view. Thus they will demand a more adequate treatment of such important subjects as absorption and secretion, urine, blood and muscle chemistry, acid-base regulation, detoxication, animal calorimetry and respiration chemistry. These very important topics are practically ignored in the text under review.

In other respects, however, the book is excellent and should make a welcome addition to our texts on biochemistry. The appearance of the printed page is clear and attractive with the reactions, diagrams and tables well set out. At the conclusion of each chapter is given a list of appropriate reviews and digests pertaining to the subject matter involved. The author has also collected a number of interesting and pertinent quotations from the scientifically minded masters of the past. An introduction has been written for this, the American edition, by Victor C. Myers.

E. G. S.

Essentials of Dermatology. By NORMAN TOBIAS, M.D., Senior Instructor in Dermatology, St. Louis University. 497 pages; 13 × 20 cm. J. B. Lippincott Co., Philadelphia. 1941. Price, $4.75.

This book is a small compend on dermatology, which has been recommended by the author for use by general practitioners and medical students. As the author states in his introduction, the description is concise, and all superfluous writing has been eliminated. There are numerous minor errors in the early part of the text, especially regarding the various biologic tests used in dermatology. These errors may prove confusing to students. The pictures are good, and are arranged in their proper position in the text. There is also a good chapter on syphilis and the treatment of syphilis, which follows the principles of the coöperative clinical group.

Collectively, this book is somewhat better than the average small text in dermatology, but it has no distinctive features.

H. M. R., JR.

COLLEGE NEWS NOTES

New Life Member

Dr. Walter J. Wilson, Sr., F.A.C.P., Detroit, Mich., became a Life Member of the American College of Physicians on June 16, 1941.

Gifts to the College Library

Book

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass.—"Medical Papers" (Bound collection of reprints).

Reprints

Dr. Otis L. Anderson, F.A.C.P., Chicago, Ill.—2 reprints;
Dr. Irving L. Applebaum (Associate), Newark, N. J.—6 reprints;
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—3 reprints;
Dr. Edward G. Billings, F.A.C.P., Denver, Colo.—1 reprint;
Dr. Albert G. Bower, F.A.C.P., Glendale, Calif.—1 reprint;
Dr. Julius H. Comroe, Jr. (Associate), Philadelphia, Pa.—1 reprint;
Dr. Orin J. Farness (Associate), Tucson, Ariz.—2 reprints;
Dr. James M. Flynn, F.A.C.P., Rochester, N. Y.—2 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—2 reprints;
Dr. Harold J. Harris (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Meredith B. Hesdorffer (Associate), Missoula, Mont.—1 reprint;
Dr. Egon E. Kattwinkel, F.A.C.P., West Newton, Mass.—1 reprint;
Dr. Moise D. Levy, F.A.C.P., Houston, Tex.—3 reprints;
Dr. Victor W. Logan, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Sydney R. Miller, F.A.C.P., Baltimore, Md.—3 reprints;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—1 reprint;
Dr. Robert J. Needles, F.A.C.P., St. Petersburg, Fla.—3 reprints;
Dr. Abe Ravin (Associate), Denver, Colo.—1 reprint;
Dr. Nathaniel E. Reich (Associate), Brooklyn, N. Y.—4 reprints;
Dr. David R. Sacks, F.A.C.P., San Antonio, Tex.—1 reprint;
Dr. David J. Sandweiss, F.A.C.P., Detroit, Mich.—2 reprints;
Dr. Charles H. Sprague, F.A.C.P., Boise, Idaho—2 reprints;
Dr. Aaron A. Sprong (Associate), Sterling, Kan.—3 reprints;
Dr. Robert T. Sutherland, F.A.C.P., Oakland, Calif.—1 reprint;
Dr. Harold Swanberg, F.A.C.P., Quincy, Ill.—4 reprints;
Dr. John W. Wilce, F.A.C.P., Columbus, Ohio—1 reprint;
Dr. Zolton T. Wirtschafter (Associate), Cleveland, Ohio—4 reprints.

The Board of Trustees of the American Medical Association has announced the appointment of Dr. Theodore G. Klumpp, F.A.C.P., Washington, D. C., as Secretary of the Council on Pharmacy and Chemistry of the Association. Dr. Klumpp will take office on July 1, 1941. Dr. Klumpp will also serve as Director of the Chemical Laboratory and Director of the Division of Foods, Drugs and Physical Therapy of the Association.

The decoration of the White Cravat with Red and Blue Borders of the Illustrious Order of the Jade was granted to Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif., by Generalissimo Chiang Kai-shek of China, on the 29th anniversary of the National Revolution, October 10, 1940. This award bore the following citation:

"For work of merit in public health in the Republic of China and among the Chinese population in San Francisco."

On May 2, 1941, Dr. Rufus S. Reeves, F.A.C.P., Philadelphia, Pa., received the 18th annual Strittmatter Award. The award consists of a gold medal and a scroll and was founded by the late Dr. I. P. Strittmatter for donation to the physician who makes the most valuable contribution of the year in Philadelphia to the healing arts. This award was given Dr. Reeves in recognition of his work as Chairman of the Annual Postgraduate Institute of the Philadelphia County Medical Society.

Dr. Ella Roberts (Associate), Philadelphia, Pa., has been appointed Medical Director of the Children's Heart Hospital, Philadelphia, Pa., to succeed Dr. Oswald F. Hedley, F.A.C.P., who has been transferred to the National Health Institute, Bethesda, Md.

At the 42nd Annual Meeting of the American Therapeutic Society held in Cleveland, Ohio, May 30–31, 1941, Dr. Louis Faugeres Bishop, Jr., F.A.C.P., New York, N. Y., retiring President, was elected a member of the Council for the succeeding five years.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., was elected President-Elect of the American Association for the Study of Allergy at the 19th Annual Meeting of the Association held in Cleveland, Ohio, June 2, 1941.

Dr. Harold G. Trimble, F.A.C.P., Oakland, has been elected President of the California Tuberculosis Association and Dr. E. Richmond Ware, F.A.C.P., Los Angeles, Vice-President. Among the Directors of the Association are: Drs. Chesley Bush, F.A.C.P., Livermore; Carl R. Howson, F.A.C.P., Los Angeles; Philip H. Pierson, F.A.C.P., San Francisco; Sidney J. Shipman, F.A.C.P., San Francisco; Rudolph H. Sundberg, F.A.C.P., San Diego; and William C. Voorsanger, F.A.C.P., San Francisco.

On May 21, 1941, Dr. Sigmund S. Greenbaum, F.A.C.P., Philadelphia, Pa., addressed the Medico-Dental Society of Atlantic City, N. J., on "Diseases of the Mouth."

The Society for Investigative Dermatology, Inc., held its 4th Annual Meeting in Cleveland, Ohio, June 3, 1941. The Presidential Address was given by Dr. J. Bedford Shelmire, F.A.C.P., Dallas, Tex. The title of his address was "Study of Sensitivity to Poison Ivy."

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, Pa., spoke on "The Present Status and Treatment of Chronic Arthritis" at the meeting of the Oklahoma State Medical Association in Oklahoma City, May 20, 1941.

Dr. John J. Weber (Associate), Brooklyn, N. Y., has been appointed Active Consulting Physician to the Kingston Avenue Hospital, Brooklyn.

On May 6, 1941, Dr. Hyman I. Goldstein (Associate), Camden, N. J., addressed the 17th Annual Meeting of the American Association of the History of Medicine, held in Atlantic City, N. J., on "The History of Ulcer of the Stomach and the Duodenum."

The State Committee of the New Jersey Gastro-enterological Society for the 7th Annual Convention of the National Gastroenterological Association, to be held in Atlantic City, N. J., during the spring of 1942, includes: Dr. Hyman I. Goldstein (Associate), Camden, Chairman; Dr. Manfred Kraemer, F.A.C.P., Newark, Vice-Chairman and Secretary; Dr. Louis L. Perkel, F.A.C.P., Jersey City, and Dr. Sigurd W. Johnsen, F.A.C.P., Passaic.

Dr. William Dameshek, F.A.C.P., Boston, Mass., spoke on "The Spleen: Facts and Fancies" at the 89th Annual Session of the Maine Medical Association, held in York Harbor, June 22–24, 1941.

Among the speakers at the annual Conference of Health Officers and Public Health Nurses, held in Saratoga Springs, N. Y., June 24–26, 1941, were:

Dr. Soma Weiss, F.A.C.P., Boston, Mass.—"Heart Disease";
Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.—"Nutrition—A Public Health Problem";
Dr. Lawrence Kolb, F.A.C.P., Washington, D. C.—"Alcoholism and Public Health."

Among the speakers at the recent annual meeting of the Medical Society of the State of North Carolina, in Pinehurst, N. C., were:

Dr. Louis H. Clerf, F.A.C.P., Philadelphia, Pa.—"Tumors of the Larynx and Hypopharynx";
Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C.—"The First Ten Years of Duke University School of Medicine and Duke Hospital";
Dr. William T. Rainey, F.A.C.P., Fayetteville, N. C.—"The Management of Congestive Heart Failure."

The Committee on Nutrition and Deficiency Diseases of the Philadelphia County Medical Society and the Philadelphia Child Health Society recently sponsored a special meeting on nutrition. Dr. Rufus S. Reeves, F.A.C.P., Philadelphia, Pa., spoke on "Nutrition—The Cornerstone of National Defense," and Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., spoke on "Medical Aspects of Nutrition."

The Pacific Northwest Medical Association held its 18th Annual Meeting in Spokane, Wash., June 25–28, 1941. Among the speakers at this meeting were:

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y.—"Diagnosis and Treatment of Infectious Arthritis, of Osteoarthritis and of Gouty Arthritis";
Dr. Louis H. Clerf, F.A.C.P., Philadelphia, Pa.—"Clinical Significance of Hoarseness and Its Importance in Cancer of the Larynx"; "Bronchoscopy in Non-tuberculous Pulmonary Disease"; "The Esophagus and Its Diseases";

Dr. William J. Kerr, F.A.C.P., San Francisco, Calif.—"Clinical Use of the Symballophone; Pathologic and Physiologic Factors in Coronary Occlusion; Treatment of Angina Pectoris."

Dr. James K. Hall (Associate), Richmond, Va., was installed as President of the American Psychiatric Association at its recent annual meeting in Richmond, Va.

Dr. Rufus S. Reeves, F.A.C.P., Philadelphia, Pa., spoke on "Nutrition and National Defense" at a meeting of the Ex-Residents and Fellows of the Robert Packer Hospital in Sayre, Pa., June 20, 1941.

Dr. Abraham M. Rabiner (Associate), Brooklyn, N. Y., has been appointed Clinical Director of the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.

Dr. Archibald A. Barron, F.A.C.P., Charlotte, was elected President of the North Carolina Neuropsychiatric Association, and Dr. Fonso B. Watkins, F.A.C.P., Morganton, Vice-President, at the recent meeting of this society.

The Utah State Medical Association held its 47th Annual Meeting June 12–14, 1941, in Salt Lake City. Among the guest speakers at this meeting were:

Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn.—"Hyperinsulinism"; "Endocrinology—A Critical Review";

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Treatment of the Anemias"; "The Hemorrhagic Diseases."

The American Neurological Association held its 67th Annual Meeting in Atlantic City, N. J., June 9–11, 1941. Dr. Norman Jolliffe, F.A.C.P., New York, N. Y., spoke on "Clinical and Chemical Studies in Wernicke's Syndrome"; and Dr. Lawrence Kolb, F.A.C.P., Washington, D. C., spoke on "Degeneration of the Primary Sensory Neuron in Pigs from Nutritional Deficiency."

The Dallas Southern Clinical Society has launched a program of courses for the continuation of medical study. Present plans of the Society are to hold these courses during June, October, and January. The first group of courses was conducted June 23–25, 1941, and the following subjects offered: Medicine—Cardiology; Surgery—Fractures; Obstetrics—Normal and Abnormal Labor; Pediatrics—Nutrition and Gastrointestinal Diseases. The courses will be conducted in the hospitals and clinics of Dallas. The Society has made an effort to limit the subjects to one particular phase of the specialty and to cover that subject thoroughly. Among those who participated in the first group of courses were:

Dr. Henry M. Winans, F.A.C.P.—"Hemodynamics of the Circulation" and "Diagnosis and Treatment of Cardiac Arrhythmias";

Dr. J. Shirley Sweeney, F.A.C.P.—"Reasons for Accepted Classification and Recommended Terminology in Heart Disease";

Dr. W. Grady Reddick, F.A.C.P.—"Roentgen Aid in the Diagnosis of Heart Disease" and "Demonstration of Bed Patients with Various Types of Heart Disease: Differential Diagnosis, Treatment, Prognosis and Discussion";

Dr. William H. Potts, F.A.C.P.—"Circulatory Function Tests";

Dr. Robert M. Barton, F.A.C.P., and Dr. Merritt B. Whitten (Associate)—"Principals and Practical Application of Electrocardiography";

Dr. David W. Carter, Jr., F.A.C.P.—"Heart Failure: Edema, Dyspnea, Cyanosis" and "The Treatment of Cardiac Failure";

Dr. Samuel A. Shelburne, F.A.C.P.—"Cardiac Clinic: Demonstration of Ambulatory Heart Patients: Differential Diagnosis, Treatment, Prognosis and Discussion";

Dr. William H. Bradford (Associate)—"General Food Requirements in Infancy: Normal, Twins, Premature, Diabetic";

Dr. John G. Young, F.A.C.P.—"Breast Feeding," "Formula Feeding" and "Use and Abuse of Laxatives and Cathartics";

Dr. John E. Ashby (Associate)—"Oral Disorders and Dentition";

Dr. H. Leslie Moore, F.A.C.P.—"Differential Diagnosis of Appendicitis."

Herbert T. Kelly, M.D., F.A.C.P., Philadelphia, Pa., participated in a symposium on the "Management of Various Types of Obesity" presented at the Spring Clinic of the Ingham County Medical Society at Lansing, Michigan, May 1, 1941.

At the annual meeting of the Pennsylvania State Dietetic Association at Philadelphia, May 22, 1941, Dr. Kelly presented a paper on "The Nutrition Program of the Medical Society of the State of Pennsylvania." He also addressed the 73rd annual convention of the Pennsylvania State Dental Society at Bedford, Pa., on June 3, 1941 on "Medical Aspects of Dentistry"; and on June 6, 1941, he addressed the Columbia County Medical Society at Bloomsburg, Pa., on "Nutritional Management of the Pre- and Postoperative Patients."

Dr. Carl J. Wiggers, F.A.C.P., professor of physiology in the School of Medicine of Western Reserve University, was awarded the honorary degree of Doctor of Science by the University of Michigan at its commencement exercises, June 21.

An authority on the physiology of the heart and circulation, in recent years Dr. Wiggers has concentrated upon phases of research in his subject, including ventricular fibrillation, the disturbance which stops the heart in acute and chronic heart diseases, in angina pectoris and coronary occlusion and in accidental electrocution; and has also conducted studies of extra-cardiac factors of circulation, the part the blood vessels play in the blood flow particularly in failure of the circulation in surgical shock and similar conditions. For this research he has had appropriations from the John and Mary R. Markle Foundation of New York and the Commonwealth Fund of New York.

Dr. Wiggers graduated from the University of Michigan Medical School in 1906, and taught there and at Cornell and in the University Medical College of New York City before joining the faculty of Western Reserve University in 1918.

Maryland Members Hold Regional Spring Meeting

The Spring meeting of the Maryland Chapter of the American College of Physicians was held at a dinner in Baltimore, May 28, 1941. There were sixty-two members present. As has been customary at the Spring meetings the major topic of discussion was the recent Annual Session of the College. Dr. Wetherbee Fort, President of the Maryland Chapter and other members who attended the Boston meeting wished to express their appreciation to the College for the delightful musical evening in Symphony Hall.

Dr. John T. King was elected President for the coming year.

Under the chairmanship of Dr. Walter L. Bierring, F.A.C.P., Iowa State Health Commissioner, Des Moines, the Iowa State Department of Health and the Iowa State Medical Society sponsored a Special Institute on Industrial Health from June 23 to 27, with a day each in Burlington, Cedar Rapids, Mason City, Sioux City and Des Moines. Dr. Lee R. Woodward, F.A.C.P., was in charge of local arrangements at Mason City. The same subjects were covered at each center or city—"The Industrial Back," "Industrial Hygiene Control Measures," "Management of Multiple Injuries," "Demonstration of Methods Employed in Industrial Hygiene," "Medical Control Measures in Industry," "Medical Relationships in Compensation" and "Medicine in Industry."

Charles W. Clarke, M.A., M.D., F.A.C.P., Executive Director, the American Social Hygiene Association, has been appointed lecturer in the School of Public Health, Harvard University, and Visiting Professor in the School of Tropical Medicine, University of Puerto Rico.

Dr. J. W. Torbett, Sr., F.A.C.P. spoke on "Some Profound Cases of Malnutrition Treated Successfully with Insulin" at a recent meeting of the 12th District Medical Society in Waco, Texas.

Dr. Joseph H. Barach addressed the Albany Medical College, Albany, N. Y. on May 29, 1941. His topic was "Inheritance and Tumors." The evening of that same day he addressed The Academy of Medicine of Glens Falls, N. Y. on the subject "Present Day Treatment of Diabetes and Its Complications."

Dr. J. C. Zillhardt (Associate), Binghamton, N. Y. was guest speaker at the Tioga County Medical Society meeting held in Owego, N. Y. on June 3, 1941. Dr. Zillhardt spoke on "Blood Transfusion and Blood Banks."

The American Gastro-Enterological Association has elected new officers as follows: Dr. Russell S. Boles, F.A.C.P., President; Dr. Sara M. Jordan, F.A.C.P., First Vice-President; Dr. A. H. Aaron, F.A.C.P., Second Vice-President; Dr. J. G. Mateer, F.A.C.P., Treasurer; and Dr. Julian M. Ruffin, F.A.C.P., Recorder.

The American Foundation for Tropical Medicine, Inc. announces the establishment of a limited number of Fellowships for the post graduate course in Tropical Medicine at The Tulane University of Louisiana. The course is given for a period of four and one half months, beginning in September of each year. A certificate will be awarded to physicians who successfully complete the course. These Fellowships are available for young, duly qualified physicians who are citizens of the Republics of Mexico, Central and South America.

In addition to the tuition fee which will be met by the Foundation, each Fellowship will furnish $700 for travel and maintenance.

Applicants for the Fellowships in Tropical Medicine of the American Foundation for Tropical Medicine, Inc., should apply to the Director of The Department of Graduate Medicine, School of Medicine, The Tulane University of Louisiana, 1430 Tulane Avenue, New Orleans, La., U. S. A. Completed application forms will be submitted to the Council of the American Academy of Tropical Medicine, who will award the Fellowships.

In view of the national defense requirements Mr. Harvey S. Firestone, Jr. has advocated the saving of all used rubber in this country. Mr. Firestone makes the following valuable suggestions about the disposition of used hospital rubber:

"It would be my suggestion that you sell your hospital's scrap rubber, including that from sheeting, hot water bottles, rubber gloves, tubing, etc., to any scrap dealer who will give you the best price for it. In that way it will find a route to the reclaiming plants and the hospital will obtain some salvage value from it. Market prices of scrap rubber fluctuate the same as do prices of any other commodities. Further, different prices for the same grades will prevail in different communities because of differences in shipping costs that must be incurred to get the rubber to points where it can be reclaimed. Speaking generally, however, the types of scrap rubber which a hospital can accumulate will vary in price from less than a cent a pound to several cents per pound, with gloves and other 'pure gum' articles commanding the higher prices. If the scrap is sorted by articles or grades of rubber, it should bring more than if sold in one bulk lot."

The Medical and Surgical Relief Committee, a nationwide organization consisting of some 300 physicians and surgeons throughout the country who collect surplus medical supplies and, when necessary, funds for the relief of civilians and armed forces in Great Britain and allied countries, have undertaken the sale of an emblem. The emblem is a lapel ornament in the form of a modified Caduceus combined with a sword of mercy and sells for $1.00. The headquarters of this Committee are located at 420 Lexington Ave., New York, N. Y.

Correction: May 1941 ANNALS, page 2147, the dates should read as follows: first paragraph, July 9, 1925; fourth paragraph, line 1, December 1923, line 5, January 20, 1925.

OBITUARIES

DR. WILLIAM HENRY WALSH

Carving for himself a unique career, after early service in the Medical Department of the United States Army and with the United States Public Health Service, Dr. William Henry Walsh brought honor to himself and to the profession of which he was a member by devoting much of his life to the betterment of hospitals. Scores of communities in the United States, Canada, and other countries are benefiting today from hospital service planned to meet their special needs with the advice and under the direction of Dr. Walsh. His fame as a consultant on hospital planning, equipment, organization and management spread to other nations, and for more than two decades he was recognized as a leading world authority on hospitals.

At a time when a few of our younger physicians may be deploring the interruption of their careers incident to military service, it is of interest to note that it was in the Army that this great medical career began. In 1898, at the age of 16, after graduation from Girard College, Philadelphia, he enlisted and served in the Medical Department of the United States Army in hospitals in Washington, Virginia and New Mexico, and in regimental duty in the Philippine Islands. That he became immediately an enthusiastic fighter in the war on disease is proved by the fact that before he was 20 years old, he was made chief sanitary inspector for the Insular Bureau of Health, and served in Manila for two years during a cholera epidemic.

Desire to be better prepared for the work which attracted him, led to enrollment in 1904 in the Medico Chirurgical College of Philadelphia and to his graduation from that school in 1909. Internship in the U. S. Marine Hospital in Baltimore and a year in the Immigration Service in Philadelphia followed. In 1911 Dr. Walsh was appointed Medical Director of the Philadelphia Hospital for Contagious Diseases. While serving in this capacity, he gave his first major talk at a conference of the American Hospital Association in 1914, on the subject, "The Hospital Superintendent—Past, Present, and Future." Published in the January, 1915, issue of *Modern Hospital,* as well as in the Transactions of the Association, it is the first of a long series of articles on hospital subjects credited to his pen.

In 1914 Dr. Walsh was appointed Chief Resident Physician at the Philadelphia General Hospital; the following year he became Medical Director of the Childrens Hospital in the same city. In 1915 he was attracted to hospital association work, becoming the first Executive Secretary of the American Hospital Association. He held that position until 1917 when he was assigned to duty in command of Base Hospital No. 58 at Camp Grant which he organized and took to France in August, 1918, serving successively as Capt. Major and Lt. Colonel. Returning to America after the war, he was appointed Secretary of the Hospital Board of the U. S. Public Health Serv-

ice, and was later in command of the Public Health Service Hospital for Tuberculosis at Markleton, Pennsylvania. In 1924 we find Lieutenant-Colonel Walsh receiving a letter of commendation from Consul George P. Waller of the American Consular Service for the "constructive executive and diplomatic ability" shown in "guiding and directing the Vicente d'Antoni Memorial Hospital at La Ceiba, Honduras, from its conception throughout its embryonic period in the brain of yourself, your architects and builders, up to the point where you delivered it on February 3, 1924, a living, functioning entity—the finest and best equipped hospital between New Orleans and Panama"—and also for care and treatment of wounded Americans and natives during the revolution in Honduras.

In 1924 Dr. Walsh resumed the secretaryship of the American Hospital Association, while pursuing part time hospital consultation service. Rapidly the demand for this special service grew, until in 1928 he was obliged to resign in order to give full time to it. In the years between 1928 and 1941, testimonial after testimonial was written expressing appreciation of his help in the planning, building, organizing and management of hospitals.

His purposeful career has ended by death, March 28, 1941. It was colorful and varied, and brought him friendships and influence in high places over a wide territory Everywhere, by his earnestness and trustworthiness, he won the kind of response from which grew impetus to greater efficiency, better service, more regard for the needs of the hospital patient.

The hospitals that he served directly through his special services, and the hospitals that were influenced less directly through his work on committees of the American Hospital Association, his talks at hospital conferences, and his numerous articles on hospital subjects, all reflect evidence of his ambition for improved practices and policy. He stimulated the entire hospital field. There will be no end to his influence. The service that he founded and the memory that he left will endure. His personal, thoughtful, kindly counsel will be missed by many of us who sought it frequently, but his example of the high type of physician who is also an able administrator and a skilled organizer will live for many others to emulate. His was truly a career of practical service that has helped to create the Modern Hospital.

MALCOLM T. MACEACHERN, M.D., F.A.C.P.,
Chicago, Ill.

DR. EDWARD WEST HOLLINGSWORTH

Dr. Edward West Hollingsworth, F.A.C.P., Oak Park, Ill., was born on April 26, 1893, in Bel Air, Maryland, the son of Roberta Y. and the late Dr. Charles A. Hollingsworth. After receiving his pre-medical education at Swarthmore College, he graduated with the degree of Doctor of Medicine from the Medical School of the University of Virginia in 1918.

He served in the Medical Enlisted Reserve Corps of the Army from January 1918 to April 1919.

Following internship at the Lenox Hill Hospital, New York City, Dr. Hollingsworth was commissioned as Assistant Surgeon (R) in the U. S. Public Health Service on January 23, 1920. He served with the U. S. Public Health Service Hospital No. 45, Biltmore, North Carolina until September 1921, at which time he was transferred to the Veterans Administration Facility, Hines, Illinois. He served continuously at the Hines Hospital in various capacities since that date and was recently Chief of the General Medical Service.

Dr. Hollingsworth specialized for a number of years in cardiology. He avidly sought after the truth in medicine and was vitally interested in the correlation of pathological material and its clinical manifestations. His opinions were respected by all members of the medical staff and his kindly approach to patients likewise endeared him to them.

Dr. Hollingsworth took an active interest in civic and medical matters. He was a Fellow of the American College of Physicians, the American Medical Association, a member of the Chicago Medical Society, American Heart Association, Chicago Heart Association and of the Central Society for Clinical Research. He was also a member of the Phi Gamma Delta Fraternity, a member of the Contract Bridge Club of Chicago, life member of the Chicago Art Institute, member of the University of Virginia Alumni Association of Chicago, of Swarthmore University Alumni Association of Chicago and a member of the Christ Episcopal Church of River Forest, Illinois. He was a supporter of and contributor to many community and welfare organizations in Oak Park and River Forest.

Dr. Hollingsworth's death from coronary thrombosis came suddenly and unexpectedly, March 15, 1941. He was honored and respected not only by the staff of the Hines Hospital, but also by the members of the profession in his community and in Chicago.

He is survived by his widow; a daughter, Irene; mother, Mrs. Roberta Y. Hollingsworth; two brothers, Dr. William Y. Hollingsworth, Commanding Officer at the Marine Hospital, Staten Island, N. Y., and Karl A. Hollingsworth of Sanysidro, California; and a sister, Dr. Roberta Y. Hollingsworth, Dean of Women at The University of Virginia.

H. F. MACHLAN, M.D., F.A.C.P.,
Chief Medical Officer, Veterans Administration, Hines, Ill.

DR. LEON THAYER STEM

Dr. L. T. Stem was born in Rover, Tennessee, in 1884. He attended the University of Tennessee College of Medicine from which he was graduated with high honors in 1909. The next two years were spent in postgraduate study, after which he entered general medical practice. Throughout his life he frequently did postgraduate work, some of which was at New York Postgraduate Medical School and some at Presbyterian Hospital, New York City. He also took a clinical European tour in 1926. During the world war he

was stationed at the Army Medical School and for some time was Staff Physician at U. S. Army General Hospital No. 19, Oteen, N. C. After his return to Chattanooga he was Chief of Staff at Pine Breeze Sanitarium for several years, and was Internist on the Staff at Baroness Erlanger Hospital, Chattanooga, until the time of his retirement. He was President of the Chattanooga and Hamilton County Medical Society in 1925 and President of the Tennessee State Medical Society in 1929–30. He was a member of the Southern Medical Society and American Medical Association, and was elected a Fellow of the American College of Physicians in 1923.

In 1934 Dr. Stem was forced to retire from active practice, because of arthritis and heart disease, at which time he moved to Sarasota, Florida, in an attempt to regain his health. In 1938 he developed a left sided hemiplegia and from then his condition gradually became worse and death occurred May 15, 1941, as a result of congestive heart failure.

It has often been said of physicians that they gave their lives for their patients, and in the case of Dr. Stem this was undoubtedly true, for he continued with his work long after he had been warned by his physicians that to do so meant irreparable damage to his health, and this in face of the fact that there was no financial necessity for him to make this sacrifice.

Until he was forced to retire, he never refused to see a patient, regardless of whether it was day or night, whether the weather was good or bad, or whether the patient was pay or charity. He had an enormous practice and his patients loved him blindly and trusted him implicitly. They depended on him for advice on all subjects. He was exceedingly kind and very tolerant of human frailties, but he did not have any patience with those who failed to live up to their word or deliberately misled him.

He was a devoted father and kind thoughtful husband. One of his four sons is a doctor and another is still in medical school. He has one brother who is also a doctor. Next to his devotion to his profession and almost equal to that for his family, his loyalty to organized medicine stands out as one of his dominant interests. The many positions which he held in various organizations were given in reward for years of unfailing interest and untiring service.

He was always helpful to younger physicians and his life was an inspiration to them as well as to all of his associates. He was a devoted friend and a considerate, courteous and wise consultant. His loss will be keenly felt.

CHARLES R. THOMAS, M.D., F.A.C.P.,
Chattanooga, Tenn.

DR. WILLIAM FITCH CHENEY

Dr. William Fitch Cheney, F.A.C.P., San Francisco, California, died on April 10, 1941. Born at Canandaigua, N. Y. in 1866, he received his B.L. at the University of California in 1885, followed by the degree of M.D.

from the former Cooper Medical College, now Stanford University Medical School. He served as Professor of Principles and Practice of Medicine at Cooper Medical College from 1898 to 1909; Clinical Professor of Medicine, Stanford University Medical School from 1909 to 1932, when he was made Clinical Professor of Medicine, Emeritus, which position he held up to the time of his death.

He was a member of the San Francisco County Medical Society, serving as President in 1905; a member of the California State Medical Association, the American Medical Association, the American Gastro-enterological Association, the American Therapeutic Society, a Diplomate of the American Board of Internal Medicine, Fellow of the American College of Physicians since February 24, 1926.

Dr. Cheney was one of the first and better known gastro-enterologists of the Pacific Coast and gained a national reputation in this field. A dignified and gentlemanly figure, he commanded the respect and admiration of his fellow physicians. He represented only the charming types of physician, who combined with professional attainments a background of culture and wide range of interests.

His heritage of intellectual attainment was passed on to his son, Dr. Garnett Cheney of San Francisco, and to the many students and interns who came in contact with him during the many years of his teaching career.

ERNEST H. FALCONER, M.D.,
Governor for Northern California

DR. JOHN DUDLEY DUNHAM

Dr. John Dudley Dunham (F.A.C.P.), Columbus, Ohio, died January 28, 1941, of coronary occlusion; aged 67 years.

Dr. Dunham received his A.B. degree at the University of Michigan in 1894 and his M.D. degree at the Ohio Medical University in 1897. His postgraduate work was done at Columbia University in New York City and at the University of Berlin.

Dr. Dunham's great interest in the medical profession is manifested by the following activities: Instructor of Bacteriology, Ohio Medical University, 1898–1900; Director of Columbus City Board of Health Laboratory, 1898–1901; Professor of Medicine, Starling Medical College, 1901–1914; Professor of Medicine, College of Medicine, Ohio State University, 1924–1929. He was a member of the medical staffs of Mt. Carmel, White Cross, and Grant Hospitals.

He was a member of the Columbus Academy of Medicine, serving as its President in 1914. He was also a member of the Ohio State Medical Association and the American Medical Association in which he had served as chairman of the Medical Section. He was a member of the American Society of Gastro-Enterology. In 1924 Dr. Dunham was made a Fellow of

the American College of Physicians and served as a Governor for the College for the State of Ohio from 1925 to 1931.

He was Major of the Medical Corps, U. S. A., from May 1918 to April 1919 and as such was chief of the Medical Service at General Hospital No. 12, Biltmore, North Carolina, and later of the United States Military Academy, West Point. At the time of his death he was a Lieutenant-Colonel of the Medical Officers Reserve Corps.

He was a member of the Phi Delta Theta Fraternity and an active member of the American Legion.

Dr. Dunham was the first physician in Central Ohio to strictly limit his practice to Internal Medicine, which he did in 1901. He was held in high esteem by his colleagues.

He is survived by his widow, two daughters, and two sons.

CHARLES W. MCGAVRAN, M.D., F.A.C.P.,
Columbus, Ohio